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THE EXPERIMENTAL PRODUCTION OF OVULATION IN THE HUMAN SUBJECT*†

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NORMAL reproduction is impossible without successful expulsion of the ripe ovum from its follicle. The subsequent development of the follicle into a gland of internal secretion is necessary for successful implantation of the fertilized ovum. This physiologic process is little understood in the human being for no one has actually seen a follicle rupture nor observed its ovum prior to its transport into the Fallopian tube. Mature follicles have been observed and studied and the classic work of Allen, Pratt, Newell, and Bland has revealed human ova washed from the Fallopian tube. Fortunately, many interesting facts concerning this process have been gleaned from experimental procedures on laboratory animals but gross differences are present in the various species. To cope successfully with the many problems in human reproduction, the fundamental process of ovulation must be better understood.

THE EXPERIMENTAL PRODUCTION OF OVULATION IN ANIMALS

Laboratory animals can be divided into two types as regards ovulation. The large majority of them ovulate spontaneously during the

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estrus period. Ovulation in these species is a normal periodically recurring event in the regular cycle. The second group, to which the rabbit and ferret belong, does not ovulate cyclically, as Heape has shown that in the rabbit ovulation takes place only after copulation. In the absence of the male, estrus persists through the entire breeding season and the only cycle found is estrus and anestrus. In these animals artificial stimuli simulating copulation, mechanical or electrical, likewise serve to produce ovulation.

In the rabbit ovulation normally occurs ten or twelve hours after copulation. The accurate timing of this physiologic event has enabled Allen to photograph the rupture of the follicle and the eruptive expulsion of the ripe ovum. Although nervous impulses apparently control the mechanism for the production of ovulation in this type of ovulating animals, the anterior lobe of the pituitary gland still dominates ovarian activity. Fee and Parkes have demonstrated that where the pituitary is removed within one hour after copulation, ovulation does not take place. Hypophysectomy later than one hour after copulation has no inhibitory effect on the ovulatory mechanism. Follicles which fail to ovulate undergo atresia. It must, therefore, be concluded that ovulation in the rabbit and ferret depends on two consecutive events, the first of which is nervous and the second endocrine. It can be theorized that the nervous stimulus results in the elaboration by the pituitary gland of hormones necessary to ovulation.

In 1927 Aschheim and Zondek in Germany, and Smith and Engle in this country, demonstrated by a series of experiments the dominant role of the anterior lobe of the pituitary gland in the maintenance and control of ovarian function. Thus, under the influence of the pituitary gland, follicles grow to maturity, discharge their ripe ova at periodic intervals, and their follicle cavities are converted into corpora lutea. Following hypophysectomy these accurately correlated events cease, all ovarian activity stops, and the genitalia slowly retrogress. Pituitary implants or extracts of the anterior pituitary gland cause renewed ovarian activity and complete recovery of the atrophied sex organs. Suitable implants or extracts of the anterior lobe of the pituitary can replace the function of the normal gland in hypophysectomized rats.

Following the discovery of the rich source of gonadotropic hormone in the blood and urine of pregnant women, it was thought that this substance represented the hormone of the pituitary gland itself. Experiments soon revealed that this anterior pituitary-like substance, when injected into hypophysectomized rats, failed to reproduce the action of the normal pituitary. Follicles did not grow nor did ovulation take place. The only activity exhibited by this gonadotropic substance was the luteinization of the theca cells of the follicle (Selye and his co-workers, and Leonard and Smith).

A gonadotropic substance, which differed from the substances hitherto described, was found to be present in the urine of women following a normal or artificial menopause. This gonadotropic substance, when injected into hypophysectomized rats, resulted in the stimulation of follicle growth so that numerous follicles reached ma-

turity but did not ovulate. Their ova remained imprisoned, ultimately degenerated, and the follicles became atretic. Hellbaum found that the pituitary glands of horses long castrated contained only this pure principle.

It is apparent from the foregoing that the anterior lobe of the pituitary gland is responsible for two distinct reactions in the control of ovarian function. These two influences may be due to a single hormone or to two distinct fractions. Experimental evidence favors the elaboration of two discrete hormones. The first is a follicle stimulating hormone, such as that obtained from the urine of women in the postmenopausal period. Under the influence of the "follicle stimulator" primary follicles grow to maturity. The second factor is a luteinizing hormone. Ovulation and the conversion of the follicle cavity into a corpus luteum depend on the concurrent action of these two fractions at a proper stage in follicle development. A pure "luteinizer" has not been isolated as yet but the gonadotropic hormone in pregnancy urine comes the nearest to being a pure "luteinizer." Ovulation in the human being probably is the result of a proper balancing of these two actions. There is little evidence at the present to theorize the existence of an ovulation center. In the human being the entire ovulatory mechanism is under endocrinal control although in nonspontaneously ovulating animals nervous stimuli probably start the mechanism for the production of ovulation.

It has been a relatively simple procedure to produce ovulation experimentally in most laboratory animals. In nonspontaneously ovulating types ovulation can be induced by the injection of most gonadotropic principles. However, attempts to reproduce this phenomenon artificially in primates and in the human female have met with very little success. Hisaw and his co-workers have achieved this in a monkey by correctly balancing and timing the injection of follicle stimulating and luteinizing extracts. No investigators have thus far succeeded in producing ovulation in women. This is probably due to the fact that specific gonadotropic hormones have not been isolated in a sufficiently pure state. Extracts of the anterior lobe of the pituitary gland which, theoretically, should be the ideal substances have not been available in a sufficient state of purity for human therapy. Ross and Hamblen have shown that gonadotropic substances derived from pregnancy urine and blood when given parenterally have failed to produce any consistent changes in ovarian activity. One can thus conclude that the artificial production of ovulation in the human being will result only from a hormone or hormones derived from extracts of the anterior lobe of the pituitary or from gonadotropic substances simulating their actions.

GONADOTROPIC HORMONE FROM MARE SERUM

Cole and Hart, in 1930, observed that for a limited period the blood of pregnant mares contains a high concentration of a gonadotropic sub-

stance. This substance reaches its maximum concentration about the 70th day of the animal's gestation. At no time does it appear in the urine. Chart 1 illustrates the concentration of this gonadotropic substance in relation to the period of gestation as determined by these authors. When mare serum is injected into immature animals it causes marked changes in the gonads, converting them into the mature state. It produces follicle growth, ovulation, and corpora lutea. Thus, this substance, injected in young Romany ewes, produced ovulation during the anestrous season, and a second injection given seventeen days later resulted in a second ovulation with estrus, followed by pregnancy. Young sows could be made to ovulate, and go into estrus, and when the animals were bred, pregnancy resulted.

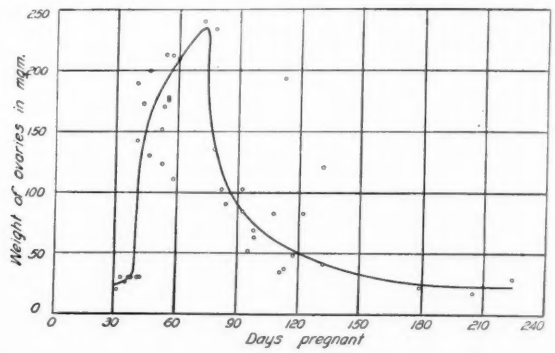

Chart 1.—Graph shows average weights of ovaries of rats injected with serum taken from mares at various stages of pregnancy. Weights include ovaries with oviducts and bursae attached. (Cole and Hart.)

These and many other experiments indicate that the gonadotropic substance present in the blood serum of the mare during pregnancy closely resembles pituitary extracts in its action. It produces follicle stimulation, ovulation and follicle luteinization. In its action it thus resembles the action of the intact pituitary (Table I).

TABLE I. REACTIONS IN OVARIES OF HYPOPHYSECTOMIZED RATS

	A.P.L. SUBSTANCE (PREGNANCY URINE)	CASTRATE OR POSTMENOPAUSAL URINE EXTRACTS	ANTERIOR PITUITARY EXTRACTS OR IMPLANTS	PREGNANT MARE SERUM
Follicle stimulation	-	++	+	++
Luteinization	++	-	+	+
Ovulation	-	-	+	+
Degenerative changes (hemorrhage and atresia of follicles)	+	-	-+	-

Biologic studies of this gonadotropic hormone have established distinct differences between it and the other gonadotropic substances. Unlike gonadotropic substance in the blood and urine of pregnant

women, the mare serum fraction is not excreted in the urine at any time during gestation. It is not ultrafiltrable through collodion membranes as are pregnancy urine substances. Thus mare serum hormone either has a higher molecular weight or possibly is combined with a large molecule which prevents it from passing through collodion membranes. It is apparently a peptide and is not soluble in the usual fat solvents used for the isolation of estrogenic hormones.

Although it has been possible to use mare serum in experimental investigations on laboratory animals, its administration is not feasible in the human being. Cartland and Nelson have successfully obtained a highly purified preparation of this gonad-stimulating substance. Their procedure consists essentially of fractional precipitation with acetone or alcohol, removal of impurities by proper adjustment of acidity, and final precipitation of the hormone fraction in the presence

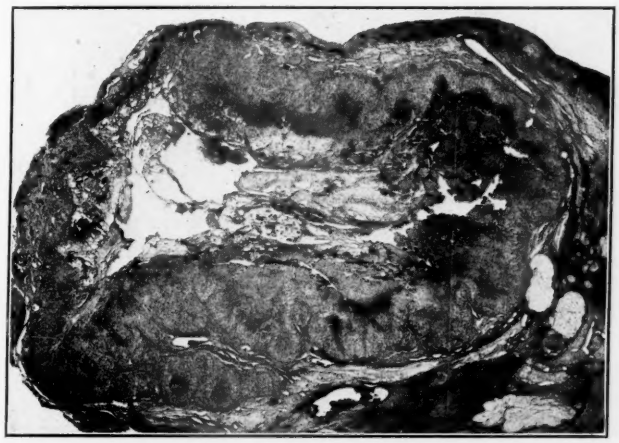

Fig. 2.—A cross section through one of the recent ovulations showing the general characteristics of a freshly ruptured follicle previously described. ×10. (Unit Number 92689.)

of increased concentration of acetone or alcohol. Yields of hormone as high as 60 to 90 per cent have been regularly obtained from the crude plasma in the form of a product representing a 130-fold purification. The hormone fractions are obtained as dry, white, water-soluble powders which are remarkably stable, furnishing a satisfactory basis for preparing sterile solutions for laboratory and clinical studies. Since this preparation is unstable under ordinary conditions it must be kept in a dry state. It is essentially free of objectionable serum proteins. Many laboratory tests indicate the lack of any toxicity.

It has been biologically assayed by a method developed in the laboratories which is based upon the increased weight of the ovaries of immature female rats injected with hormone as compared with those of uninjected controls. The rat unit has been defined as the total dose of hormone which, given in divided daily subcutaneous doses in twenty-one- to twenty-three-day-old female rats weighing 30 to 40 gm., will

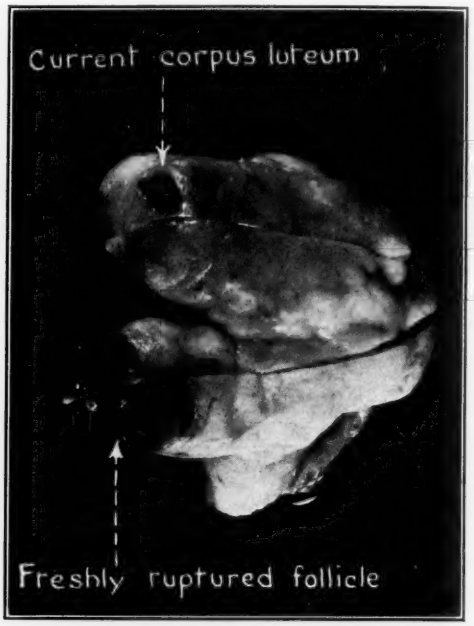

Fig. 3.—Gross view of the ovary showing recently ruptured follicle as well as the current corpus luteum (twenty-first day of menstrual cycle). Note the hemorrhagic character of the recently ruptured follicle.

Unit Number 146184. Aged 33 years. Menstrual cycle, regular 27-day type. Endometrium, late progestational type. Day of cycle when hormone was administered, twenty-first. Time elapsed from the administration of hormone to removal of ovary, 16 hours. Amount of gonadotropic hormone injected, 60 units.

Fig. 4.—Cross section through the recently ruptured follicle showing the granulosa thrown into numerous folds and marked hemorrhagic extravasation into central cavity and beneath granulosa. (Unit Number 146184.)

produce by the fifth day a pair of ovaries weighing 65 mg., which is 5 times the weight of the ovaries in the uninjected controls. It is noteworthy that in rats the response of the ovaries varies according to the amount of hormone injected. Small doses cause maturation and ovulation of a few follicles, and little or no growth of the remaining primary follicles. On the other hand, the administration of large doses results in the development of numerous maturing follicles, luteinization of unruptured follicles, but no ovulation.

EXPERIMENTAL PRODUCTION OF OVULATION IN THE HUMAN BEING

About two years ago we became interested in the gonadotropic fraction obtained from the urine of pregnant mares, because experi-

Fig. 5.—Cross section through the current corpus luteum showing the well organized luteal border and old hemorrhage in central cavity. (Unit Number 146184.)

mental evidence indicated that this fraction was likely to produce ovulation in the human being. In our earlier experiments we administered the fraction both subcutaneously and intramuscularly with varying results. Previous experimental work indicated to us that the use of this substance was likely to be most successful when administered intravenously. The available patients were carefully tested for protein sensitization, and the hormone was then administered intravenously. Women who were to be subjected to laparotomy for a variety of pathologic conditions were chosen for this work. Many of our subjects were at the period in life when there is a rapid decrease

Fig. 6.—Gross photograph of ovary showing recent ovulation and current corpus luteum. Note the hemorrhagic character of the freshly ruptured follicle and the rupture point sealed by a gelatinous blood-tinged plug.

Unit Number 39004. Aged 31 years. Menstrual cycle, irregular. Endometrium, early proliferative. Day of cycle when hormone was administered, sixth. Time elapsed from the administration of hormone to removal of ovary, 20 hours. Amount of gonadotropic hormone injected, 50 units.

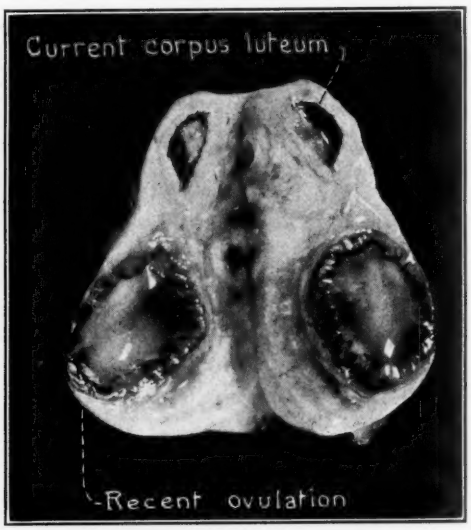

Fig. 7.—Cross section of the newly ruptured follicle showing the wavy border of granulosa cells and the follicle cavity almost completely distended by gelatinous, slightly blood-tinged fluid. (Unit Number 39004.)

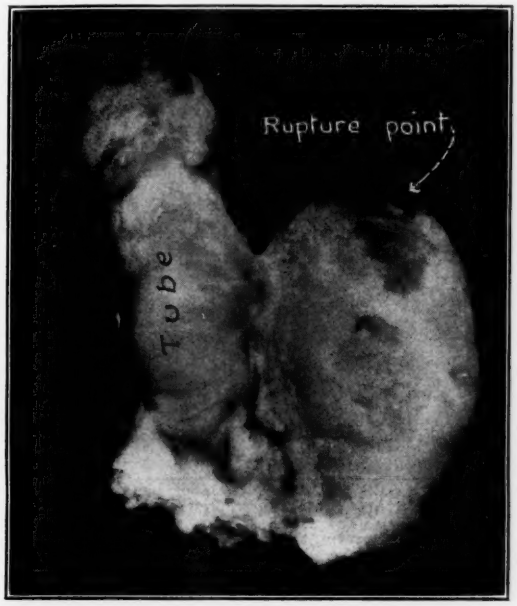

Fig. 8.—Gross view of one of the recent ovulations showing the site of rupture of the follicle. Close inspection of this fresh rupture point showed a pinkish-gelatinous fluid exuding from it.

Unit Number 64164. Aged 22 years. Menstrual cycle, 14- to 21-day type. Day of cycle when hormone was administered, fifteenth. Time elapsed from the administration of hormone to removal of ovary, 17 hours. Amount of gonadotropic hormone injected, 60 units. Ovaries showed two recent ovulations and current corpus luteum.

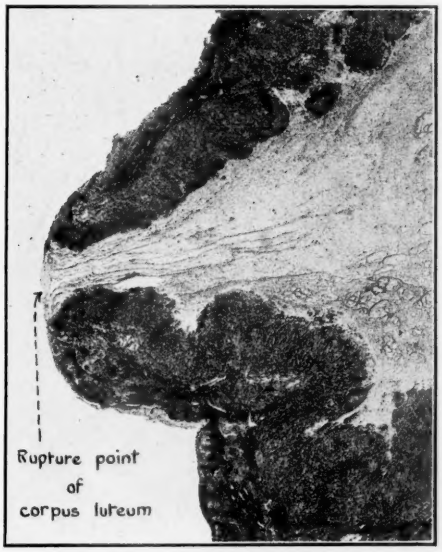

Fig. 9.—A cut section through this rupture point showed the cavity partially filled with a bloody fluid. Histologic examination revealed no luteal transformation. No fibroblasts had migrated through the granulosa layer. (Unit Number 64164.)

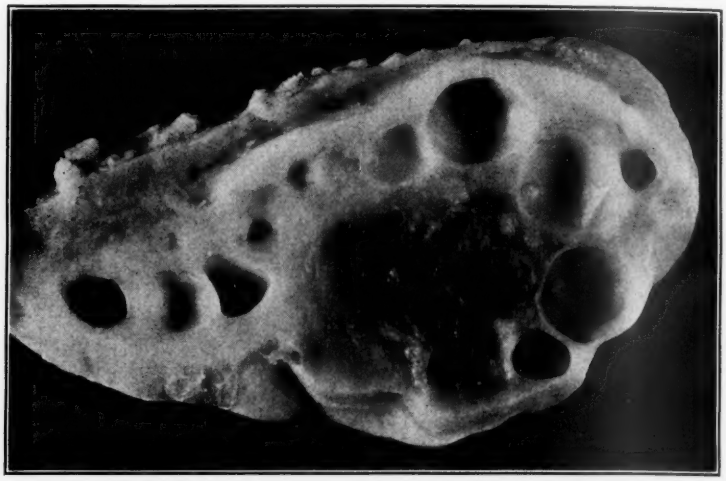

Fig. 10.—Gross view of ovary containing recent ovulation. The follicle walls were almost completely collapsed so that the folds were numerous. The small cavity contained a small amount of hemorrhagic fluid. The entire follicle presented a reddish, hemorrhagic appearance.

Unit Number 26755. Aged 38 years. Menstrual cycle, irregular. Endometrium, menstrual phase. Day of cycle when hormone was administered, seventh. Time elapsed from the administration of hormone to removal of ovary, 22 hours. Amount of gonadotropic hormone injected, 60 units.

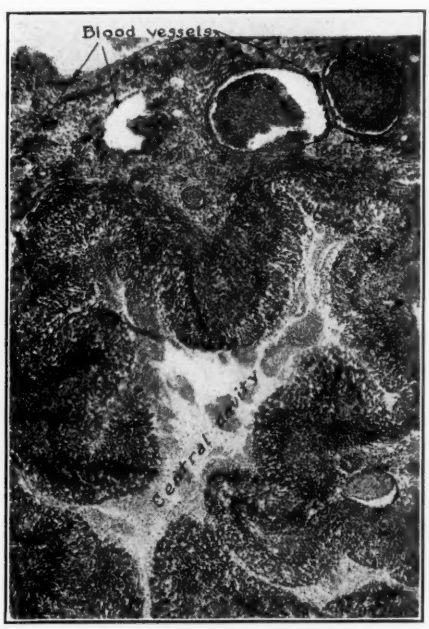

Fig. 11.—A higher magnification of a portion of the corpus luteum showing the relatively unaltered appearance of the granulosa cells and the marked vascularity and congestion of the surrounding ovarian stroma and the theca interna. ×65. (Unit Number 26755.)

of ovarian activity. Others had pathologic conditions which would mask any results which might be obtained. However, it was absolutely necessary to examine the ovaries in situ and to subject them to careful histologic study to determine the effectiveness of the preparation as judged by the reactions induced in the ovaries. The time interval from the administration of the substance to the time when the ovaries were inspected and removed was varied. Evidence concerning the reactions of the ovaries to the substance at different times in the ovarian cycle was likewise accumulated. Table II presents a résumé of the patients who received mare serum gonadotropic substance.

DISCUSSION

From the foregoing table and illustrations it is evident that recent ovulation was present in approximately half of the patients to whom

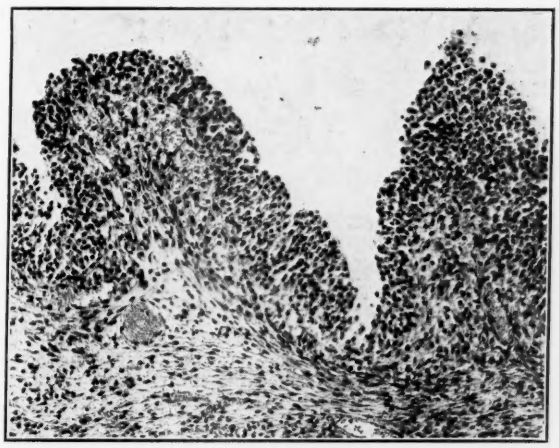

Fig. 12.—A section of the wall of the recently ruptured follicle showing the early proliferation of the granulosa cells. They still retain the follicular characteristics showing no luteal transformation. No fibroblasts have migrated into the cavity from the theca interna. Groups of theca interna cells stand out rather prominently. ×180.

Unit Number 162189. Aged 45 years. Menstrual cycle, 28-day type. Endometrium, early proliferative phase. Day of cycle when hormone was administered, eleventh. Time elapsed from the administration of hormone to removal of ovary, 17 hours. Amount of gonadotropic hormone injected, 60 units.

this substance was administered. To make certain that an ovulation is of recent origin, it is almost always necessary to obtain histologic sections of the corpus luteum. It is difficult to estimate the age of a ruptured follicle by gross inspection alone. In many instances the current corpus luteum which represented the patient's normal follicle activity was present in addition to the recent corpus luteum. This was additional evidence that the recently ruptured follicle was artificially produced by the gonadotropic substance. Furthermore, in a number of instances more than one corpus luteum of recent origin was present, thus suggesting that more than one follicle can be made to ovulate by administering adequate amounts of this substance.

TABLE II. RÉSUMÉ OF FINDINGS IN A GROUP OF PATIENTS WHO RECEIVED MARE SERUM HORMONE

	AGE	MENSES		NO. OF UNITS	HOURS ELAPSED	NO. OF OVULATIONS	HISTOLOGIC STUDIES				
		INTERVAL	INJEC. DAY OF CYCLE				CORPORA LUTEA		MATURE FOLLICLES	ATRETIC FOLLICLES	ENDOMETRIUM
							NEW	OLD			
1	44	IR.	2	60	18	1	1		++		Early proliferative
2	47	21	2	50	22	1		1		++	Early proliferative
3	37	28	3	60	16				++	+	Early proliferative
4	28	22-24	3	60	15	1		1	+		None
5	37	33	5	70	40						Early progestational
6	31	IR.	6	50	20	1	1		+		Early proliferative
7	42	28	7	60	65	2	1	1			Early proliferative
8	40	30	7	60	40	1	1				Late proliferative
9	38	IR.	7	60	23	2	1	1			Late menstrual
10	35	25	9	60	17				++		None
11	44	28	11	50	23	3	2	1	++		Early proliferative
12	45	28	11	60	17	1	1			++	Early proliferative
13	30	28	12	60	18	1		1		+	Late proliferative
14	42	27	13	60	22				++		Glandular hyperplasia
15	37	25-33	13	50	13				+	+	Glandular hyperplasia
16	39	23	14	60	42	1		1	+		Progestational
17	28	24	14	50	38	3	3		+		Early proliferative
18	41	24	15	60	42	1		1	++		None
19	22	14-21	15	60	17	2	2				None
20	36	28-31	16	90	76	2	1	1			None
21	43	28	16	60	24	1		1	++	++	Early progestational
22	39	28	21	60	22	1		1	++		Progestational
23	33	27	21	60	16	2	1	1			Late progestational
24	37	28-31	22	60	22	2	1	1			Progestational
25	27	28	22	60	23	1		1	+		None
26	38	28	22	60	16	1		1		+	Early progestational
27	40	28	23	60	45	1		1	++	+	Late progestational
28	32	24	25	60	20	1		1			Progestational
29	37	28	26	60	10	1		1			Late progestational
30	47	IR.	27	60	15				+	++	Glandular hyperplasia
31	42	28	28	60	32	3		2	+		Late progestational
32	46	Metrorrhagia		60	15	1	1				Inactive
33	30	Metrorrhagia		60	38	2	2				Proliferative
34	46	Metrorrhagia		50	64	2	1	1			Late proliferative
35	31	28-30	18	60	16	3	3	Stigma			
36	37	IR.	18	60	18	1					

In evaluating the effect of gonadotropic hormone it was necessary to establish the exact age of the corpora lutea present in the ovaries. Gross and histologic studies of our material revealed earlier stages in the formation of the corpora lutea than heretofore published. The best collections of early corpora lutea rather accurately dated are those described by Allen, Pratt, Newell, and Bland. Their criteria of age were followed.

Grossly, the majority of these corpora lutea showed distinct points of rupture, either hemorrhagic in character or exuding a bloody fluid, or a blood-tinged gelatinous substance. In only two follicles were there distinct plugs and a distention of their cavities by a blood-tinged gel. A slight amount of blood-tinged fluid was present in most of the follicle cavities.

Histologic examination revealed the walls of the follicles collapsed and greatly folded. In most instances the granulosal cells of the follicle seemed little altered from the prerupture stage. No apparent luteinoid changes could be discerned. In several instances the early stage of luteal hypertrophy was present. The "streaming out" effect of the coagulum suggestive of secretory activity on the part of the granulosa was present in the majority of the corpora lutea. There was no migration of fibroblasts into the granulosa layer or evidence of vascularization. A careful comparison of these corpora lutea with those described by Allen and his co-workers indicates that the majority of our corpora lutea were less than eighteen hours old and few as old as thirty-six hours. Their age was well within the period of time which elapsed between the administration of the gonadotropic hormone and the time of the removal of the ovary in question.

In the illustrations the gross and microscopic characteristics of a few of these early corpora lutea are pictured. A comprehensive study on the development of the human corpus luteum will be published at a later date.

The endometrium was obtained and studied in most of the cases. It was impossible to correlate the stage of endometrial development with the menstrual data in many instances, for all of these patients presented pathologic changes of the genital organs necessitating the pelvic surgery. Furthermore, irregular bleeding was the outstanding symptom in many of the patients.

Although most of our patients received about 60 units in a single dose, the results obtained by using the larger doses have not been determined as yet. In experimental animals it has been found that large doses of mare serum are likely to produce unusual enlargement of the ovaries without corpora lutea. Thus, the dosage required for excessive enlargement is much greater than that required to produce ovulation. We believe that it has been possible to provide the necessary impulse for ovulation in these patients by the intravenous administration of this gonadotropic hormone principle. Snyder has shown that early in pregnancy the ovaries of rabbits do not respond to small amounts of gonadotropic hormone repeatedly administered

subcutaneously or intravenously. On the other hand, he was able to induce ovulation in these animals by a single intravenous administration of a large amount of hormone.

The duration of time that elapsed from the administration of the substance until ovulation was produced was unusually short. We have

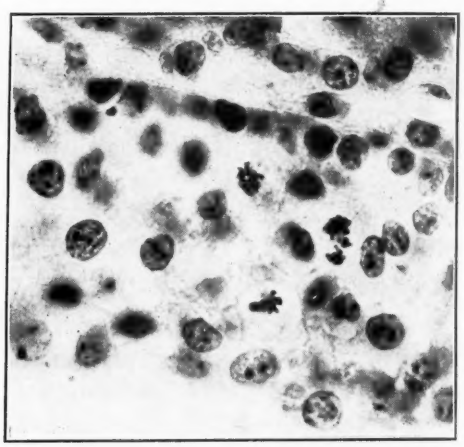

Fig. 13.—The wall of a large unruptured follicle showing the active proliferation of the granulosa as a result of the administration of gonadotropic hormone. Note the numerous mitotic figures.

Unit Number 154313. Aged 44 years. Menstrual cycle, regular 28-day type. Endometrium, early proliferative phase. Day of cycle when hormone was administered, eleventh. Time elapsed from the administration of hormone to removal of ovary, 23 hours. Amount of gonadotropic hormone injected, 50 units.

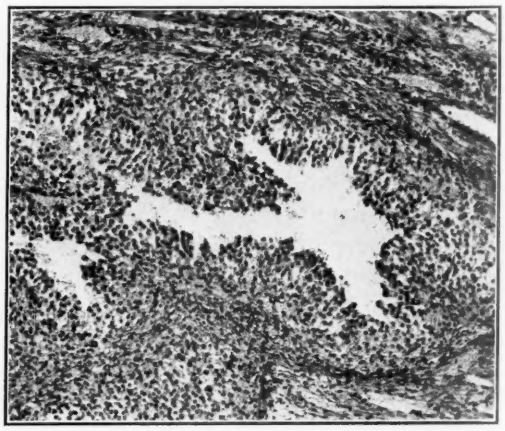

Fig. 14.—The granulosa cells appear as in the mature follicle prior to its rupture. Theca interna cells can be seen in the folds between the granulosa border. ×140. (Unit Number 154313.)

been led to believe that the process of ovulation in the human being extends over a period of several days or longer during which time the follicle slowly reaches maturity and ultimately, some time in the mid cycle, ruptures and discharges its ripe ovum. It is probable that in many of our experiments maturing follicles were already present, so

that completion of the process resulting in ovulation was very rapid. On the other hand, in the women who were in the latter half of the cycle, maturing follicles ordinarily should not have been present, and yet we found recent ovulations with equal frequency during this period. We can thus theorize that this substance is capable of causing rapid follicle growth, and that these follicles rupture, release their ova and are converted into corpora lutea all within the space of twenty-four to thirty-six hours. Experimental evidence lends weight to this theory. For example, the rabbit normally ovulates about ten hours after copulation, or after the administration of a suitable gonadotropic substance.

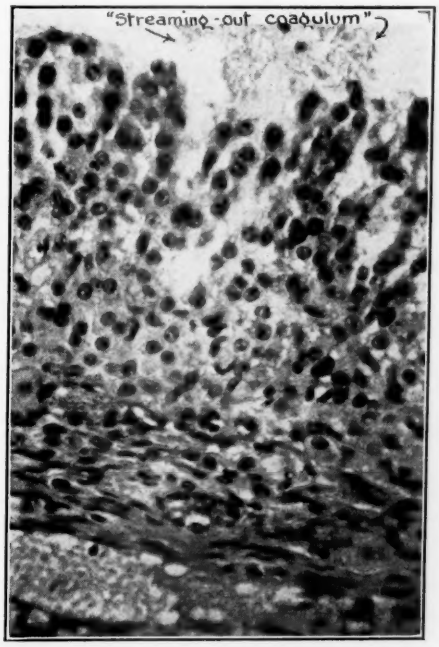

Fig. 15.—The coagulated substance extending from the granulosa cells has been described as a "streaming-out" phenomenon. The individual granulosa cells show no evidence of luteinization. No fibroblasts have penetrated into the cavity. ×525. (Unit Number 154313.)

It should be noted from Table II that the majority of recent ovulations were found in women between the fifth and thirteenth day, and between the seventeenth and the twenty-fifth day of their cycles. In some of these women it was impossible to date the cycle. The significance of this fact is as yet not understood. It should also be noted that in three women who had metrorrhagia and no definite rhythm to their bleeding, ovulations were present in all. This fact is of importance in that it may point the way to a clinical use for this substance. However, in three cases among this series where the endometrium showed typical glandular hyperplasia, no ovulations occurred. The significance of these observations is not yet clear.

The clinical application of this experimental work presents certain problems. The majority of the group of patients used in this work were probably having normal ovarian activity and periodic ovulations. To produce artificial ovulation in women with normal ovaries may be less difficult than to do so in women who have little or no ovarian activity. The therapy of this new gonadotropic material involves the treatment of patients in whom ovarian failure has resulted in a lack of follicle development and an absence of normal ovulation with their concomitant menstrual abnormalities or infertility. In these women the dosage of the hormone, the interval, and the method of its administration will determine to a large measure the success of the therapy.

Much laboratory experimentation indicates that the amount of hormone sufficient to stimulate growth of follicles may not be sufficient to produce ovulation. Too large an amount of gonadotropic substance causes the formation of many atretic follicles and the imprisonment of their ova but no ovulation. We have some clinical evidence that the most effective mode of administration is to give two or three intramuscular injections of 15 or 20 units at daily intervals to be followed by a single intravenous administration of the same or a larger amount. Thus, follicles can be stimulated to grow to maturity at which stage the intravenous administration provides the stimulus necessary to cause ovulation. These and many other problems will have to be worked out by prolonged clinical investigation.

In general, clinical administrations of gonadotropic substances have met with very little therapeutic success. Most of them have not been isolated in a sufficiently pure form so that they can be used in the human being. Those that have been purified to this extent have been ineffective in the production of changes in the ovaries. The reports of the successful use of some of these gonadotropic substances have been based on casual observations and have not been substantiated by careful workers. Ross and Hamblen, in a recent report, concluded that gonadotropic substances are not available in sufficient concentration to provide desirable therapeutic results.

Judging from the results of these investigators, substance from pregnancy urine will probably find little place in therapy. The source of hypophyseal glandular extracts is obviously limited. On the other hand, mare serum provides a concentrated and abundant source for a gonadotropic substance which apparently stimulates normal physiologic changes. It will be necessary to do a great deal more work to determine just how this substance fits into our glandular therapeutic armamentarium.

CONCLUSIONS

1. It has been possible for the first time to produce ovulation in women by the intravenous use of a gonadotropic hormone derived from serum of pregnant mares.

2. This hormone has been isolated in such an advanced state of purity that its administration by the intramuscular or intravenous route is devoid of danger, provided that suitable safeguards are established.

3. Biologically, this gonadotropic hormone resembles extracts and implants of the anterior lobe of the hypophysis but differs chemically and biologically from all other gonadotropic substances heretofore studied.

4. These experimental ovulations have provided the earliest human corpora lutea yet described.

5. Clinically, this gonadotropic hormone should prove efficacious in the therapy of patients in whom follicle growth and ovulation are at fault.

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The author reports on 27 fibroadenomas removed during pregnancy and lactation, or present during that period and removed at varying intervals following the cessation of lactation. It was observed that the tumors were modified by pregnancy and lactation, and that the changes produced in them were similar to those occurring simultaneously in the surrounding normal breast tissue, probably are of hormonal origin.

J. P. Greenhill.

A STUDY OF THE WATER, SODIUM, AND ENERGY EXCHANGE DURING THE LATTER PART OF PREGNANCY*

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IT HAS been suggested that retention of water may be the cause of the toxemias which occur late in pregnancy (pre-eclampsia and eclampsia). Cummings[1] found that the incidence of toxemia was greater in those patients who gained more than thirty pounds during pregnancy. He further pointed out that rapid and excessive gains in weight during the eighth and ninth months were the results of fluid retention, and appeared several weeks before definite edema could be demonstrated. Wieloch[2] states that water retention occurs universally in his cases of toxemia of pregnancy. Arnold and Fay[3] have reported the prevention and control of eclampsia by restricting the fluid intake to the amount of urine the patient excretes and by further dehydrating the patient by the use of magnesium sulphate and hypertonic solutions of dextrose.

It is well known that water is often retained in cases of toxemia of pregnancy in amounts sufficient to cause gross edema. Indeed, the opinion is quite prevalent that not only in cases of toxemia, but in *all* pregnant women water is retained in excess of the amount needed to form the fetus and its adnexa and the new maternal protoplasm. Fink[4] claims that in 95 per cent of his cases of pregnancy there is some degree of "occult or gross edema." Stander[5] and more recently Oberst and Plass[6] have shown that there is an increase in blood volume and a dilution of the blood during pregnancy.

From observations such as these it is apparent that a knowledge of water metabolism during pregnancy is needed. Except for studies of the blood, all approaches to the study of water metabolism during pregnancy have been entirely inadequate. Recently, as a result of the researches of Newburgh and his associates[7, 8] and Peters,[9] it has been possible to deal directly with the problem of water metabolism.

We have started investigations planned to throw more light on the problems of water metabolism during pregnancy and the suggested disturbance of water balance associated with the toxemias. The first study, reported herein, concerns primarily the exchange of water and sodium during the last two months of normal pregnancy and a short period post partum. Data regarding the exchange of nitrogen and total energy, obtained during the course of this investigation, are included in this communication.

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METHOD

The subject of this study was an American girl, aged 17 years, who was in her first pregnancy. She was 157.5 cm. in height. Her average pregravid weight was 46.5 kg. She had been in splendid health before this pregnancy. During the second and third months she had only slight nausea and occasionally vomited, otherwise she felt entirely well throughout the pregnancy.

Beginning on the seventieth day before delivery she was fed a simple weighed diet consisting of milk, eggs (boiled), bread, butter, jelly, corn flakes, canned pears and grapefruit, and sugar. The diet was identical day after day. It contained 82 gm. protein, 91 gm. fat, and 247 gm. of carbohydrate; the calorific value was 2,133 or about 46 calories per kg. of pregravid body weight. There was an excess of alkaline ash equivalent to approximately 12 c.c. normal alkali.

On December 27 (at the end of four weeks) the diet was changed slightly; salmon was substituted for the eggs, and different fruit was served. The dietary formula, however, was practically unchanged: protein 82 gm., fat 93 gm., carbohydrate 230 gm., calories 2,085. This diet was served daily until January 26, when it was changed by the addition of 110 gm. of 40 per cent cream, altering its composition to protein 85 gm., fat 137 gm., carbohydrate 233 gm., calories 2,498. Beginning February 6, jelly was omitted and the amount of butter was increased to keep the calorific value the same. This was the last change made in the diet.

Metabolism studies were begun on the sixty-second day before delivery and continued throughout the remainder of pregnancy and for a short period in puerperium. During most of the time the metabolism periods consisted of seventy-two hours; for a short time at the beginning and post partum, twenty-four hourly periods were employed. Heat production was determined by the method of Newburgh, Wiley and Lashmet,[10] which depends on the measurement of insensible loss of weight. The *actual* percentage of total heat eliminated by the vaporization of water was determined* in the manner described by Newburgh and others,[11] and this factor was used in calculating total heat production from insensible loss of water. Since the patient was quantitatively fed, energy balance could be calculated. Nitrogen balance was determined by analysis of ingesta and the urine and feces by the Kjeldahl method. One tenth gram was added to the measured, daily nitrogen excretion, to represent the nitrogen loss from the skin and its appendages.

Complete water balance was determined according to the technique of Wiley and Newburgh.[8] This method deals with all the known increments of water exchange: as sources of water the water of food, water drunk, water resulting from the oxidation of foods, and preformed water are determined, and the amounts of water eliminated in the urine and stool, and as vapor are measured separately.

Sodium balance was calculated by comparison of the intake and the urinary excretion of this element. The amount of sodium in the ingesta and urine was determined by the Butler-Tuthill[12] method. Wiley and Wiley[13] have shown that the fecal excretion of sodium is negligible. Sodium eliminated through the skin was ignored in this study. To increase the sodium intake 5 gm. of NaCl were fed daily, in capsules, from February 1 through February 6.

There was no lactation post partum. The water of the lochial discharge was included along with fecal water in the considerations of water exchange post partum.

RESULTS

The entire course of pregnancy was normal in every respect. The total gain in weight was very close to 9 kg. During the last two months there was a gain of 3,793 gm. Visible edema was never present. The pregnancy ended at full term by the spontaneous delivery of a healthy male baby weighing 3,229 gm. Throughout the

*Drs. L. H. Newburgh, M. W. Johnston, and J. M. Sheldon made this determination.

study the patient cooperated splendidly; she ate all of the food each day except on the day of delivery and two days early in post partum. Vomiting, proteinuria, and glycosuria never occurred, hence the intakes and the urinary and fecal excretions of the substances studied were satisfactorily determined.

Details of the water balance and the net balance of sodium, nitrogen, and energy, and the body weight are presented in Table I. In Chart 1 the body weight and the exchange of nitrogen, energy, sodium, and water are shown graphically.

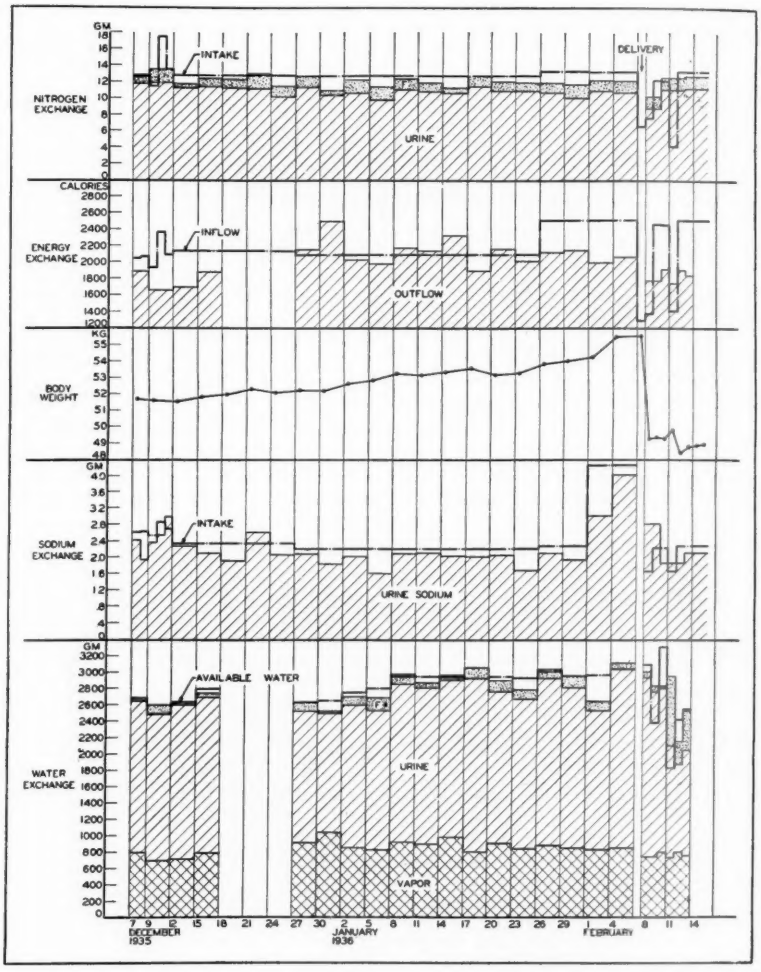

Chart 1.—The nitrogen, energy, sodium, and water exchange and body weight during the last two months of pregnancy and early post partum. *F*, in each case represents fecal excretion.

From December 18 through December 26, because of improper regulation of the room temperature, sweating, crying spells, and an acute upper respiratory infection, insensible loss of weight could not be accurately determined. As a result water and energy exchange could not be calculated during this time. On the day of delivery due to sweating and other unusual events, it was impossible to make the usual observations. In Table II the items accounting for the reduction in body weight (6,256 gm.) on the day of delivery are presented.

TABLE I. DETAILS OF THE WATER EXCHANGE, AND SUMMARY OF THE SODIUM, NITROGEN AND ENERGY EXCHANGE

DATE	WATER EXCHANGE										SODIUM BALANCE GM.	NITROGEN BALANCE GM.	ENERGY BALANCE CAL.	BODY WEIGHT AT END OF PERIOD GM.
	WATER OF FOOD GM.	WATER DRUNK GM.	WATER OF OXIDATION GM.	PREFORMED WATER GM.	TOTAL AVAILABLE WATER GM.	WATER OF URINE GM.	WATER OF FECES GM.	WATER VAPOR GM.	TOTAL WATER ELIMINATED GM.	WATER BALANCE GM.				
														51,642
Dec. 7, 8	2995	1802	493	5	5295	3696	77	1596	5369	- 74	0.91	-0.37	331	51,573
9-11	4927	1936	659	-53	7469	5375	318	2097	7790	-330	0.25	2.08	1434	51,509
12-14	4819	2486	658	-74	7889	5684	32	2149	7865	24	0.22	3.27	1306	51,796
15-17	4853	2803	757	-23	8390	5731	178	2384	8293	97	0.71	0.97	749	51,946
18-20	4841	2768	*	*	*	4311	421	*	*	*	1.32	1.33	*	52,331
21-23	4856	2894	*	*	*	5000	355	*	*	*	-0.79	-0.38	*	52,064
24-26	4834	2904	*	*	*	3733	295	*	*	*	0.88	3.97	*	52,220
27-29	5049	2020	822	- 2	7889	4839	270	2732	7841	48	0.36	0.19	-235	52,213
Dec. 30-Jan. 1	5062	2071	936	-90	7979	4340	88	3157	7585	394	1.13	5.48	-1242	52,600
Jan. 2-4	5074	2472	778	-32	8292	5216	314	2565	8095	197	0.54	1.63	161	52,809
5- 7	5061	2668	761	-78	8412	5092	460	2497	8049	363	1.82	4.06	322	53,251
8-10	5067	2986	827	-19	8861	5840	348	2750	8938	- 77	0.32	1.18	-277	53,146
11-13	5077	3002	811	-47	8843	5720	208	2693	8621	222	0.28	2.60	-142	53,387
14-16	5074	3038	877	-75	8915	5762	111	2945	8818	97	0.55	4.44	-740	53,505
17-19	5080	2968	728	- 6	8770	6370	430	2389	9189	-419	0.62	0.01	578	53,092
20-22	5065	2999	817	-42	8839	5588	387	2716	8691	148	0.55	2.36	-197	53,243
23-25	5073	2991	761	-54	8771	5513	311	2521	8345	426	1.64	2.80	265	53,752
26-28	5260	3053	803	-87	9029	6102	330	2659	9091	- 68	0.43	4.06	1193	53,902
29-31	5243	2970	780	-102	8891	5851	460	2562	8873	18	0.95	4.77	1422	54,143
Feb. 1-3	5212	3015	751	-73	8905	5089	321	2494	7904	1001	3.65	3.10	1584	55,395
4-6	5198	3226	771	-74	9121	6508	241	2573	9322	-201	0.78	3.26	1396	55,435
7	870	141	*	*	*	†	512	*	*	*	†	†	*	49,179
8, 9	2937	2084	447	11	5479	4216	137	1483	5836	-357	-1.80	-0.61	280	49,158
10	1722	1344	241	1	3308	1999	26	798	2823	485	0.36	-0.41	542	49,725
11	965	493	211	160	1829	1380	858	723	2961	-1132	-0.16	-8.37	-329	48,251
12	1745	457	240	-22	2420	1090	278	792	2160	260	0.46	0.85	621	48,591
13	1741	598	232	-18	2553	1279	483	763	2525	28	0.18	0.60	690	48,704

*Water vapor could not be accurately determined.
†Amniotic fluid mixed with part of urine on this day.

DISCUSSION

Chart 1 shows the nitrogen retention during this study. Throughout the last sixty-two days of pregnancy, 50.8 gm. of nitrogen were retained; the average daily retention was 0.82 gm. This is distinctly less than was found by Hunscher and others[14] in their own investigation (3.1 gm. daily), and less than that observed (2.28 gm. daily) by other investigators as reported by Hunscher[15] in a review of the literature. The reason for the difference is undoubtedly the result of a number of factors including the size, state of nutrition, and physical activity of the mothers prior to pregnancy, the size of the babies, and the nitrogen and calorific values of the diets. For instance, Hunscher's patient was 68.5 inches tall and normally weighed 135 pounds, in contrast to the smaller size of our subject. Moreover, Hunscher's subject received an average of 19 gm. nitrogen and 3,400 calories daily in contrast to 13 gm. nitrogen and about 2,200 calories fed our subject. The protein in our diet was of good biologic value, and the amount of nitrogen retained was more than sufficient for the formation of a fully developed fetus and its adnexa.[16] It should be noted that from January 26 until delivery on February 7, when the calorific value of the diet was greater than previously, the nitrogen retention was also slightly greater. During early post partum, the nitrogen exchange was irregular; later there was a slight retention of nitrogen.

TABLE II. KNOWN ITEMS OF WEIGHT LOSS DURING THE DAY OF DELIVERY

	GRAMS
Baby	3,229
Placenta, cord, and membranes	433
Amniotic fluid	354
Blood	124
Vaginal discharge	105
Urine	1,401
Feces	440

A study of the energy exchange reveals several interesting facts. From December 7 through December 17, the energy inflow exceeded the energy outflow by 3,820 calories, an average of 347 calories daily. Since the water exchange during this period was slightly negative, the increase in weight (304 gm.) recorded during this time resulted from the formation of new protoplasm. A simple calculation will prove that this statement is true. Assuming that the amount of glycogen in the body remains constant and that true water balance exists, changes in body weight will be the result, almost entirely, of changes in the amount of protein and fat in the body. From December 7 through December 17, 5.95 gm. of nitrogen were retained. This represents 37 gm. dry protein (N × 6.25) which will require the association of 111 gm. water (3 gm. of water per 1 gm. dry protein). This 37 gm. of protein accounts for the storage of 148 calories. Since the energy exchange shows a retention of 3,820 calories during this period, 3,820 minus 148, or 3,672 calories must have been stored as fat. The weight of the fat stored is 3,672 divided by 9.54 or 383 gm. With this amount of fat, 38 gm. of water are stored (0.1 gm. water per 1 gm. fat). The body weight during this period should be increased by the sum of these items (37 plus 111 plus 383 plus 38) or 569 gm. if water balance obtained. However, during this period, the elimination of water exceeded the intake by 283 gm., hence, the net gain in weight would be 569 minus 283, or 286, which very closely approximates the observed increase in body weight, 304 gm. The small difference is readily understood when one considers the deposition of inorganic material and glycogen in the growing fetus, which has been ignored in this calculation.

From December 27 through January 25, the energy transformation exceeded the inflow by 1,510 calories, 50 calories daily. During this same period there was a retention of 1,399 gm. of water in excess of that used in the formation of new protoplasm. This accounts for most of the increase in weight (1,532 gm.) observed during this period. Because of the slightly negative energy balance beginning January 26 the calorific value of the diet was increased by 415 calories daily, making the

energy balance again positive. This accounts for the gain in weight (391 gm.) during the following six days when there was almost exact water balance.

Following parturition the energy transformation lessened due to the confinement to bed, and to the loss of that increment of total metabolism previously contributed by the fetus.[17]

Chart 1 shows retention of sodium throughout almost the entire period of study. It must be kept in mind, however, that urinary sodium is the only excreted sodium measured. Freyberg and Grant[18] have found that from 65 to more than 200 mg. of sodium are eliminated through the skin of normal adult individuals during normal activity, in twenty-four hours. It is reasonable to assume that our patient eliminated approximately 0.1 gm. of sodium daily through the skin, in which case there was less sodium retained than represented in our data. During the periods of greatest gain in body weight (December 30 to January 1, January 5 to 7, January 23 to 25, and February 1 to 3) sodium (and water) was retained in amounts greater than usual. In order to study the effect of an abrupt increase in the intake of sodium, 5 gm. of NaCl were fed daily from February 1 through February 6. There was a retention of 3.65 gm. of sodium and of 1,001 gm. of water in excess of that used in the formation of new tissue, during the first three days of this period. During the second three days, only 0.78 gm. of sodium was retained, and the elimination of water exceeded the intake by 201 gm. On the first day after the high intake of sodium was stopped, the elimination of sodium could not be accurately measured because parturition occurred. The sodium balance was negative on February 8 and 9; on February 10 it again became slightly positive, indicating that the elimination of the added sodium had been completed. This response to feeding NaCl is identical to that observed in a normal nonpregnant individual by Wiley and Wiley.[19]

Newburgh's method for determining insensible loss of weight gave gratifying results in this subject. During the last forty-two days of pregnancy the amount of water vaporized is strikingly constant. Likewise, during the first six days post partum the water vaporized was very nearly the same each day.

When one considers the exchange of water along with the body weight, it is observed that just as in the case of sodium, there was retention of water during each period in which the weight increased more rapidly than usual. Likewise, each time the body weight decreased (January 8 to 10, and 17 to 19), negative water balance was recorded. One thousand and one grams of water were retained in excess of that needed for the formation of new tissue during the first three days of the period of high sodium intake (February 1 to 3); this retained water, along with the positive energy balance which obtained during this time, accounts for the sharp increase in body weight observed (a gain of 1252 gm.).

In computing water balance, four sources of water must be considered. Three sources always contribute to the total, namely, water drunk, water of food, and water formed by the oxidation of the metabolic mixture. To the sum of these three increments is *added* a fourth source, the "preformed water" liberated, if body tissue is burned, as part of the metabolic mixture; if new tissue is formed, the water used in the formation of it is *subtracted* from the sum of the first three sources. So the value for "preformed water" may be *plus* or *minus*. The algebraic sum of all four items is therefore *not* merely the water intake, but is "available water." It is this available water with which the total water lost from the body is compared in computing water balance as presented in Table I and Chart 1.

During the fifty-three days of pregnancy when water exchange was measured 151,491 gm. of water (the sum of all water drunk, water of food, water of oxidation, and water liberated by destruction of body tissue) needs to be accounted for. The total amount of water lost from the body by all avenues of excretion during this time was 148,679 gm. Thus, there was a gross retention of 2,812 gm. of water. Of this 2,812 gm. of water, 931 gm. entered into the formation of body protein and fat, leaving 1,881 gm. of water still to be accounted for. Our subject responded to a sudden increase in sodium intake in a normal manner, which is at first a retention, and later, a corresponding loss of water. However, the occurrence of parturition did not give us the opportunity to record the loss of water. Therefore, it is necessary to subtract the amount of water retained, 1,001 gm., in order to arrive at

the disposition of water during normal pregnancy. After this subtraction is made (1,881 minus 1001) 880 gm. of water remain.

To understand where this water is located, one must consider many possibilities. The amount of amniotic fluid might be increased. Beck,[20] however, states that commonly there is no increase in amniotic fluid after the seventh month, in fact it usually decreased in amount.

It is well known that maternal blood volume usually increases during pregnancy.[5] In our subject the volumes of maternal blood and plasma were measured* at intervals (during the last two months of pregnancy) and were found to be:

DATE	PLASMA VOLUME C.C.	TOTAL BLOOD VOLUME C.C.
Dec. 7, 1935	2,340	4,140
Dec. 27, 1935	2,380	4,100
Jan. 17, 1936	2,400	4,210
Feb. 7, 1936 (early in labor)	2,160	3,660

From these data we cannot ascribe any of the retained water to the maternal blood.

The weight of the fetus normally is doubled during the last two months of intrauterine life. Accordingly it is reasonable that the fetus in our subject added at least 1,500 gm. to its mass during the period of study. Since the water content of the normal human fetus at full term is approximately 70 per cent of its weight, it can be estimated that 1,050 gm. of water were added to the fetus during the period of investigation. Of the total amount of water used in the formation of new protein and fat (931 gm.), the portion entering into the formation of *fetal* tissue cannot be directly determined. However, Macy and Hunscher[16] state that during the last two lunar months of pregnancy an average of 43 gm. of nitrogen are retained by the human fetus. Assuming the fetus in our subject added this amount of nitrogen to its mass, then 806 gm. water were added along with it. Accordingly, 244 gm. of water (1050 minus 806) were added to the fetus in excess of that united with the protein made. Thus, it is reasonable, ignoring the small amount of water stored with fat tissue (0.1 gm. water per 1 gm. fat) that no more than 636 gm. of water (880 minus 244) were retained by the *maternal* organism throughout this last two months of pregnancy, in excess of that amount used in formation of new tissue ("superhydration"). This amount of water retained is only 1.3 per cent of the immediate postpartum body weight, and averages 12 gm. daily. Since fluctuations of 500 gm. of body water are common, and a gain or loss, up to 1,000 gm., has been observed[21] in a normal male individual when the intake of food and water, and the physical activity, were constant, we do not consider the retention of 634 gm. of water by our subject significant of an important "superhydration."

SUMMARY AND CONCLUSIONS

The nitrogen, energy, sodium, and water exchanges observed during the last two months of normal pregnancy, and for a short period post partum, are presented. Changes in body weight are discussed in relation to the energy, sodium, and water balance. The larger fluctuations in body weight resulted from significant changes in the body water, which accompanied parallel shifts in sodium balance. When the intake of sodium was abruptly increased by feeding 5 gm. of sodium chloride daily for six days, there was a marked retention of sodium and water during the first three days; the sodium and water balance were negative during the first few days after the sodium in-

*Blood volume determinations were made by Dr. F. H. Bethell.

take was lowered to its previous level. This entire response is identical with that observed when the intake of sodium chloride is increased in a nonpregnant normal adult. These observations indicate to us that the same factors that govern water balance in normal nonpregnant individuals would be of similar importance during pregnancy. The most important of these is the regulation of the intake of inorganic elements, chiefly sodium. Prevention of retention of abnormal amounts of sodium should therefore prevent significant superhydration, regardless of the intake of water.

During fifty-three days of the last two months of pregnancy, there was a gross retention of 2,812 gm. of water; however, after deducting the amount entering into the formation of body tissue, that retained as a result of suddenly increasing the intake of sodium, and, after allocating the proper amount to the fetus, only 636 gm. could be considered as "maternal superhydration." This is not beyond the normal fluctuation of body water.

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DISCUSSION

DR. WILLARD R. COOKE, Galveston, Texas.—This experiment is unique in establishing an element not considered previously, namely, the normal status of the individual in late pregnancy.

The excessive retention of water in late pregnancy is of considerable significance and may be taken into account in two directions; first, that the extreme retention of water as indicated by edema and rapid excessive gain in weight may mean the onset of toxemia; the other is that such storage of water up to a certain point is a protective device of nature against the dehydration which may accompany labor. A great many of us in studying patients in the prenatal period, have encountered cases that tend to show the error of too great dependence upon this finding as indicative of impending toxemia, in that many women who gain rapidly in weight are, as far as we are able to determine by subsequent study, perfectly normal. We see, on the other hand, toxemic patients who do not gain in weight rapidly or excessively; this "dry" eclampsia is likely to be very severe. I have always thought that water storage in late pregnancy is primarily an effort of nature to supply the

patient with water to compensate for the loss by sweating, hyperventilation, and the inability to obtain water during labor. In the lower animals this mechanism seems to function perfectly. Personally, I think it is possible to pick up positive evidences of toxemia earlier in other ways than by the observation of an excessive gain in weight. What to do about excessive storage of water in the absence of toxemia we do not know, since we have had no idea of what the process is.

DR. HAROLD S. MORGAN, LINCOLN, NEB.—Dr. Freyberg and his co-workers have shown convincingly that the pregnant woman reacts to changes in water balance as does the normal nonpregnant woman. The translation of these thoughts into the realm of clinical obstetrics is intriguing. We have constantly before us the picture of the pregnant woman suddenly showing a marked increase in weight. This increase in body weight we have been taught to consider an early manifestation of toxemia, appearing in most cases before there is any rise in the blood pressure.

It has been our experience that it is entirely possible to handle this type of patient along the lines indicated by Newburgh and Freyberg in other communications. It is a rule in our practice to weigh every obstetric patient at every visit to the office. The patient is, of course, weighed without her clothes. If perchance a sudden excessive gain in weight is noticed during the last trimester, the patient is promptly placed on a restricted regime which may be detailed as follows: (1) All salt removed from the diet. (2) Intake and output of fluids approximated as closely as possible. (3) Increased rest, fresh air, and sedation if necessary. (4) Return to the office in forty-eight hours.

If at the end of forty-eight hours she has not lost her retained water, 10 gr. of ammonium chloride, three times a day, are administered.

Our usual experience is that patients showing this syndrome will after four or five days of careful attention, lose their water and simply by keeping on a salt-free diet and water imbalance, i.e., slightly lower intake than output, progress normally throughout their pregnancy. It is to be admitted that the odd patient will not respond and will slowly develop a rising blood pressure with a later albuminuria. It is our feeling that this patient is in a precarious condition and serious consideration should be given to the question of termination of pregnancy.

DR. FREYBERG (closing).—It would be interesting to call to your attention that Straus has reported the production of the signs and symptoms of toxemia of pregnancy resulting from water retention induced by feeding various sodium salts when hypoproteinemia exists. In the absence of hypoproteinemia the feeding of sodium salts did not produce symptoms of toxemia, and the results were similar to those in our patient when sodium chloride was fed.

Dr. Morgan noted that the treatment of his patients with toxemia of pregnancy that had edema was being carried out along the lines suggested by our experience in patients with edema accompanying chronic nephritis. In these patients we consider two points as being important. First, we make every effort to prevent the retention of sodium by feeding a low sodium diet and by having the reaction of the ash of that diet neutral, because we have observed that an alkaline ash diet will favor the retention of water. Second, we make every effort to remove the sodium that has been retained. When retained sodium is excreted, a corresponding amount of water is liberated and removed from the body and the edema decreases. The manner that has been found most satisfactory in our experience for removing sodium is the use of ammonium chloride. When these measures are carried out it is not necessary to restrict the intake of water. One can think of a situation in which the sodium acts as a sponge in the water, and when there is no sodium the water will not be retained even though 5,000, 6,000, or 7,000 c.c. of water might be taken into the body. We think it is more important to regulate the inorganic constituents, especially sodium, entering the body rather than restrict water. In patients who have severely damaged kidneys, it is not wise in our experience to restrict the intake of water.

ONE-STAGE OPERATION FOR RESECTION OF THE RECTOSIGMOID AND RECTUM FOR CARCINOMA (WITH OR WITHOUT HYSTERECTOMY)*

I. Combined Anterior and Posterior Resection

II. Combined Abdominoperineal Resection

J. P. Pratt, M.D., Detroit, Mich.

(From the Department of Gynecology and Obstetrics, Henry Ford Hospital)

THE ideal treatment of carcinoma of the rectum and rectosigmoid is complete extirpation with restoration of continuity of the bowel. No artificial anus can equal the comfort of the natural mechanism. The value of a method will be determined by low mortality, high rate of operability, possibility of wide excision and consequently a high percentage of cures. A one-stage procedure is preferable if the hazard of operation is not increased. Difference in pathology and anatomic arrangement prevents accepting a single standardized procedure. A combined anterior and posterior resection or abdominoperineal resection is applicable to nearly every carcinoma of the bowel below the level at which a Mikuliez operation is possible. When the uterus is involved, hysterectomy may be included in the resection. These operations involve procedures which are closely akin to other gynecologic problems. The method here reported is the result of experience with 40 patients operated upon since 1924.

METHOD

Preliminary biopsy of the growth through the proctoscope verifies the diagnosis. Deep x-ray therapy precedes the resection by four to six weeks. During this period the general health of the patient is treated with particular attention to under-nutrition and anemia. The patient's blood is grouped and matched with a suitable donor. For two days preceding the operation, the patient is restricted to a low residue, high caloric diet. The lower bowel is prepared by cathartics and enemas.

The abdominal part of the operation is similar for both the posterior and perineal resections. Hysterectomy may be combined with either, but delivery of a large mass is easier through the perineal incision.

The incision preferred is paramedian or median extending from the umbilicus to the symphysis. In obese patients, it may be necessary to extend the incision above the umbilicus. A right or left rectus incision is satisfactory, but in general, it gives a less adequate exposure. Since the abdominal procedure is completed without opening the bowel, the incision may be closed without drainage.

A preliminary cecostomy should be performed for decompression when an existing obstruction does not yield to simple measures. The time elapsing between cecostomy and resection varies with the individual but should be long enough to

*Presidential address read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists at Dallas, Texas, October 14 to 16, 1937. (Illustrated by Cinema.)

The privilege of treating the women with carcinoma of the rectum and rectosigmoid is due to the courtesy of R. D. McClure, M.D., Surgeon-In-Chief, Henry Ford Hospital.

The assistance of my associates, Merrill Smeltzer, M.D., and Milo Ritter White, M.D., is acknowledged.

permit the condition of the patient to improve to a degree consistent with undertaking the larger operation. The cecostomy is far enough away from the midline to easily avoid contamination. Spontaneous closure of the cecostomy occurs unless special precautions are taken to keep it open.

Exploration of the abdomen includes inspection of the liver, glands along the abdominal aorta, the regional glands, the location and fixation of the growth. Involvement of the liver or aortic glands prevents any probability of cure of the carcinoma but does not preclude the desirability of a resection for the comfort of the patient. Co-existing lesions in the pelvis are examined and treated as indicated. In one instance, the omentum was incarcerated in an inguinal hernia, the aortic glands extensively involved and the growth in the sigmoid was fixed to the sacrum and pelvic wall, rendering the case inoperable. In addition, there was a large carcinoma of the right ovary which was easily removed. In another instance

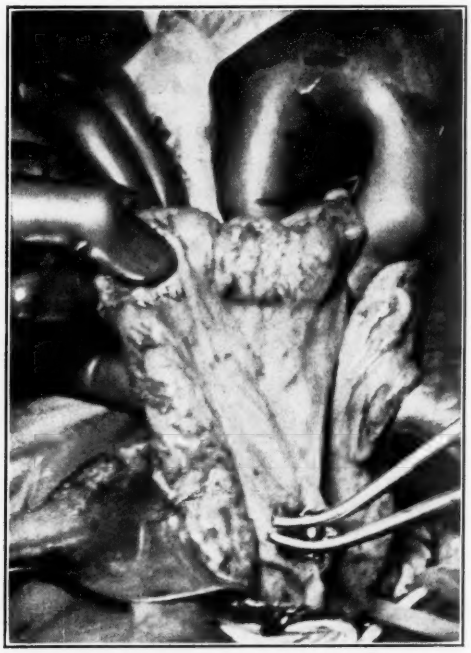

Fig. 1.—Photograph to show section and ligation of the vessels far away from the bowel to preserve the anastomotic loops.

the aortic glands were extensively involved, but the rectosigmoidal growth was operable and was removed. The appendix, both tubes and ovaries and the uterus were also removed, because there was an acute and chronic inflammation of these structures.

Preservation of adequate circulation to the portion of bowel to be retained is essential. This can be readily determined by the change in color of the bowel after the vessels are sectioned. There is considerable individual variation in distribution of the vessels to the sigmoid. In case too much of the bowel is accidentally devitalized, a colostomy may be done. The pattern of the blood vessels can be demonstrated by transillumination of the mesentery but is obscure in some obese patients. When the mesentery of the sigmoid is stretched, the location of the superior hemorrhoidal and inferior mesenteric vessels is indicated by the fold of mesentery which contains them. It is desirable to section the vessels near their origin and as far from the bowel as possible in order to preserve the anastomotic loops (Fig. 1). If the vessels in the fold of the mesentery are obscured by fat,

they may be exposed by incising the peritoneum and dissecting the fat. Ligation of the inferior mesenteric blood vessels early in the resection controls most of the bleeding. The middle hemorrhoidals are encountered late in the mobilization of the rectum. It is simpler to ligate these during the anterior part of the resection.

Mobilization of the bowel is begun by sectioning the mesenteric vessels. It is continued by incising the peritoneum of the mesentery along each side close to the bowel except at the level of the growth where a wider margin should be taken (Fig. 2). If the uterus is to be retained, the lateral incisions of the peritoneum are connected by a transverse incision at the level of its reflection from the bowel to the cervix and vagina. If complementary hysterectomy is included, the incision of the peritoneum is continued into the incision of the broad ligaments. The ureters are not exposed or endangered if the peritoneal incision is kept close to the bowel. The next procedure is the loosening of the bowel by blunt dissection with the fingers and scissors (Fig. 3). The loose fat yields readily except at the level

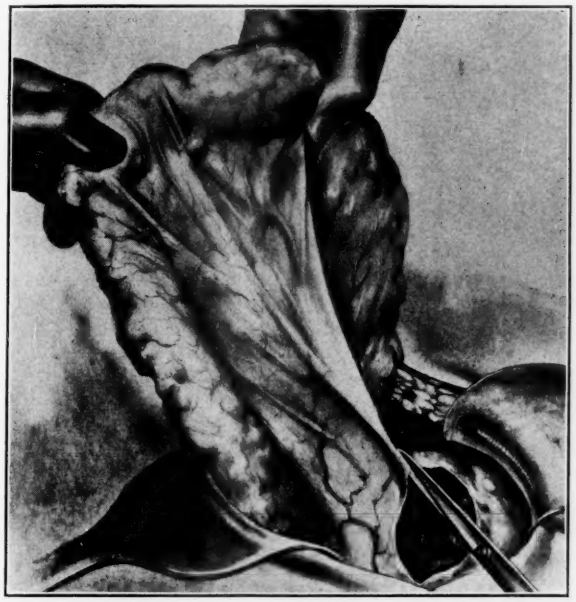

Fig. 2.—Showing the incision of the peritoneum close to the bowel except at the level of the growth. This leaves an abundance of peritoneum for subsequent closure of the abdominal cavity from the denuded pelvis.

of the growth. The pathologic variations and the anatomic relations determine the procedure of loosening the growth in each individual case. The dissection from the abdomen is carried to the tip of the coccyx or below it. While freeing the bowel from the sacrum, special attention is given to the lateral sacral vessels, particularly where they enter the sacral foramina. Injury to the veins at this point may lead to uncontrollable hemorrhage.

The pelvic peritoneum is closed after all bleeding is controlled and the loose bowel tucked into the pelvic cavity. If hysterectomy has been performed, the closure is begun at the bladder. Without hysterectomy, the closure is begun at the cervix. Ample space is left at the upper end of the suture line to permit free passage for the sigmoid. In obese patients with a small pelvis, the line of incision is filled and no closure is needed. The break in the peritoneum is thus repaired and the abdominal cavity separated from the raw area of the denuded pelvis (Fig. 4). The omentum is drawn into the lower abdomen, and the incision in the abdominal wall is closed without drainage.

For the posterior resection, the patient is placed in Sims' or lithotomy position. An incision is made between the anus and the tip of the coccyx. The fascia and levator muscles are divided in the midline, opening the free space in the pelvis made by the abdominal dissection. The loose bowel is drawn through the incision and the redundant loop excised giving the growth a wide margin (Fig. 5). The

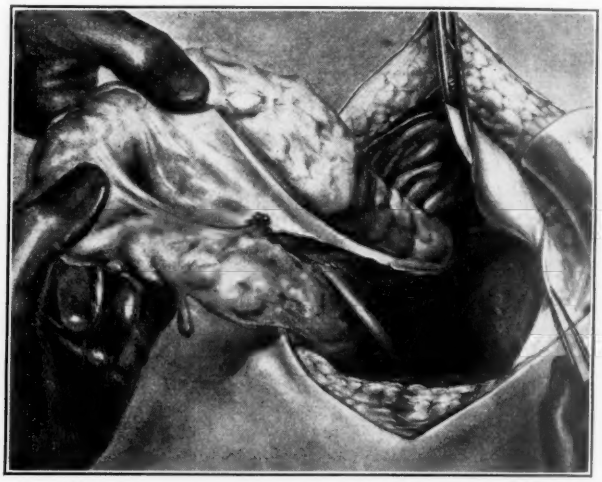

Fig. 3.—Showing the mobilization of the bowel in the abdomen and pelvis. Through the abdominal incision this dissection is continued to the tip of the coccyx.

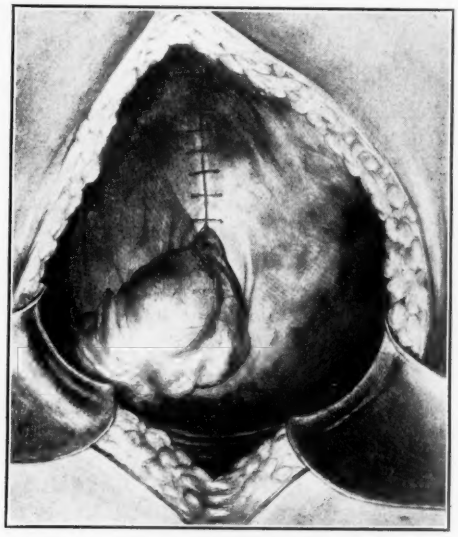

Fig. 4.—Showing the closure of the peritoneum. The bowel has been tucked into the pelvis. The pelvis is isolated from the abdominal cavity.

cut end of the sigmoid is anastomosed to the cut end of the rectum by a few sutures. Many sutures interfere with the circulation of the bowel and result in sloughing. The anastomosis, when returned to the pelvic cavity, lies directly within the incision which provides a vent during healing and restoration of continuity of the bowel. A single drain is placed beside the bowel to promote the escape of serum

and blood from the pelvic cavity. This is apparently not important and may be omitted. The drain is removed in twenty-four to forty-eight hours. The posterior incision usually closes spontaneously. Secondary closure is necessary in some instances.

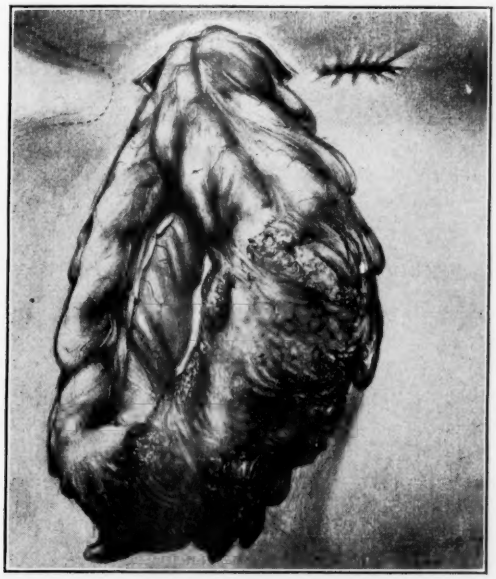

Fig. 5.—Showing the loop of mobilized bowel drawn through the incision between the anus and the tip of the coccyx.

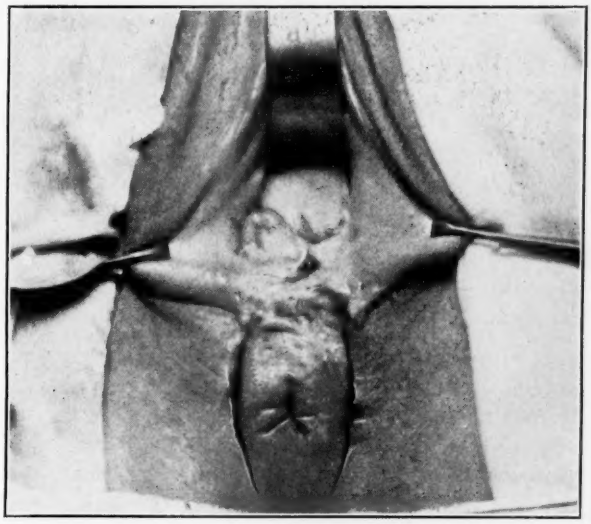

Fig. 6.—Photograph (retouched) to show an exaggerated midline episiotomy extended around the anus. An extensive growth involved the rectum to a point 2 cm. above the anus in this case.

The perineal resection is combined with the abdominal operation when the rectum and anus are involved by the growth. The perineal operation varies according to the location and character of the growth. An exaggerated midline episiotomy may

be extended around the anus to include as much skin as is indicated (Fig. 6). A portion of the posterior vaginal wall may be excised if that structure is involved. The resection may include the anus, sphincters, the greater part of the levators and their fascia as indicated. The dissection is continued upward from the incision in the skin and vaginal mucosa to meet the dissection already completed in the abdomen. The anus, rectum, and rectosigmoid are now free and are drawn through the perineal opening (Fig. 7). The redundant bowel is excised. A rubber tube is sutured into the cut end of the sigmoid. The perineum is repaired loosely. The bowel may be attached to the skin edge by a few sutures. Emphasis is placed on a wide excision and a loose closure. The perineal like the abdominal colostomy functions best when there is a wide opening. A drain placed beside the bowel provides an exit for any serum or blood that accumulates in the pelvic cavity (Fig. 8). If the bleeding has been controlled, the drain is not needed longer than twenty-four or forty-eight hours. In a few instances the drain came out during the transfer

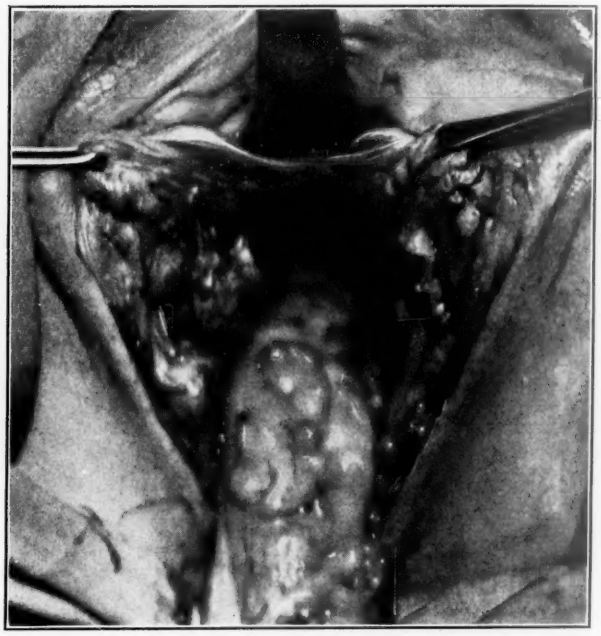

Fig. 7.—Photograph (retouched) to show the liberation of the bowel completed and drawn through the perineal opening.

from the operating table to the room without any apparent harm to the patient. The catgut sutures holding the tube in place dissolve after a few days. The incision has been protected in the meantime from local soiling. Healing has advanced by this time to protect against the spread of infection.

Hysterectomy combined with the resection is essential if the uterus is involved by the growth or shows any other important pathologic change. A complementary hysterectomy is useful in some cases to facilitate the operation by providing a better exposure. It adds very little to the operative procedure and, in fact, may shorten the operating time. Any type of complete hysterectomy to which the operator is accustomed may be chosen. Delivery of the uterus attached to the bowel offers no difficulty in the abdominoperineal resection. The limited size of the incision in the combined anterior and posterior resection may complicate the delivery with the uterus attached. This factor should be considered in choosing the type of operation. Closure of the vaginal vault when hysterectomy is combined with the

abdominoperineal resection is similar to the same part of the operation in vaginal hysterectomy. The vagina is closed from above when hysterectomy is combined with the anterior and posterior resection.

The amount of tissue that can be removed by either of the operations is almost unlimited. The growth can be given a wide margin. The regional lymphatics and those accompanying the superior hemorrhoidal vessels are included in the excision. The prime requisite (radical excision) of a satisfactory operation for cancer of the rectum and rectosigmoid is easily accomplished.

The postoperative care includes an immediate transfusion in all cases. A suitable donor whose blood has been matched with the patient is available as soon as the operation is completed. Surgical shock has rarely been encountered, although it was

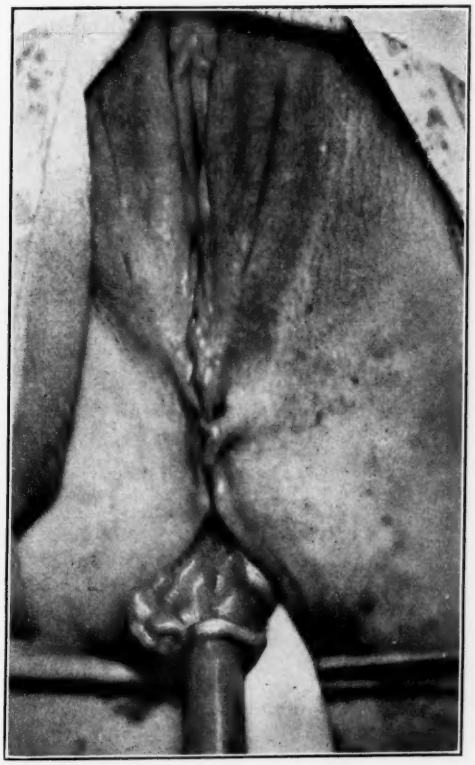

Fig. 8.—Photograph showing the perineum closed, a tube sutured into the cut end of the sigmoid and a drain placed beside the bowel to permit the escape of serum from the pelvic cavity.

responsible for one operative death. In this instance some difficulty was experienced in obtaining a suitable donor until surgical shock was manifest. It is an extensive operation at best; therefore, blood transfusion is an excellent preventive measure. Many patients might not need the transfusion, but it seems good judgment to give the blood rather than wait to see if it is needed.

The diet is similar to that given in other abdominal operations. Solid food is withheld for two days, then a low residue diet is preferred. The patients are often already debilitated and require a liberal diet to promote wound healing. Oil is given freely to keep the stools soft. Enemas can be given if indicated but are seldom required because drainage from the bowel is free.

The tube in the cut end of the sigmoid prevents local soiling of tissue until the sutures absorb and the tube drops out. By that time healing has progressed suf-

ficiently to prevent infection of the wound. In the posterior resection, drainage through the incision appears after a few days and mild local infection occurs which causes some soreness, but the infection has not spread upwards to the pelvic cavity. As healing of the anastomosis progresses, the continuity of the bowel is re-established and drainage through the incision ceases.

Healing of the posterior incision is usually spontaneous. Secondary closure has been necessary in two instances. The period of healing varies with the individual. It is a matter of weeks. While the duration of local inflammation is generally limited to a few days, one case developed an abscess in the subcutaneous tissue which drained

Fig. 9.

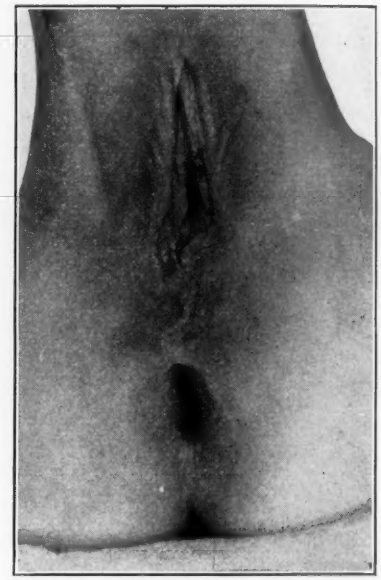

Fig. 10.

Fig. 9.—Photograph of the perineum of the first patient in whom the combined anterior and posterior resection was done. This photograph was taken thirteen years after the operation.

Fig. 10.—Photograph of the perineum two months after abdominoperineal resection. The bowel retracted but the epithelium grew in from the skin to meet it.

through the incision. Since the incision is in the midline, the tissue tends to fall together. The resulting scar is minimal. The anus retains a natural appearance (Fig. 9).

Healing of the perineal incision varies with the extent and character of the excision. Suture of the cut edge of the skin to the cut end of the sigmoid promotes quicker healing, but there is the danger of further retraction of the bowel. It may be desirable to leave some of the bowel protruding beyond the skin. After healing

is complete, the redundant bowel can be removed flush with the skin. The longitudinal muscles of the sigmoid contract causing a thickened ring of circular muscle which serves as a sphincter. Even if the bowel sloughs above the skin margin, the epithelium of the skin and bowel unite later to line the canal (Fig. 10). The perineum has a remarkable immunity to infection.

DISCUSSION

The outline of operations presented does not assume that the ideal treatment for carcinoma of the rectum and rectosigmoid has been found. It offers a choice of procedures which can be applied to almost any growth of the bowel below that level at which a Mikulicz operation can be performed. Possibility of variation in the method as the operation proceeds, extends the application to advanced growths.

Formerly, my conviction was that a colostomy was essential to a wide excision. One patient challenged that idea unintentionally.

A woman of 44 presented herself in 1924 for treatment of a carcinoma of the rectosigmoid. She refused operation if she were compelled to have a colostomy. In order to persuade her, the nature of the lesion was explained and her future predicted if she did not have the operation. Persistent refusal of the colostomy led to doing a one-stage anterior and posterior resection with preservation of the sphincters. Her recovery and thirteen years of comfort have stimulated the attempt to extend the usefulness of a one-stage resection without colostomy.

Carcinoma of the rectum and rectosigmoid is relatively less frequent in women than in men. During the last thirteen years, the one-stage resection has been done in only forty women. This series is too small to permit drawing any sweeping conclusions. Critical analysis of results is essential, however, to determine the value of the operation and to suggest modifications to be tried. Rather than present detailed case reports of all the patients, it seems more pertinent to consider briefly the six operative deaths.

1. This patient, aged 56, was in good health and general physical condition. Her lesion was early and operable. She was in good condition when she left the operating room and was not given a transfusion. Shock developed four hours later, and the patient died before a transfusion could be arranged. In retrospect, this was a preventable death if transfusion had been given earlier. Since this occurrence every patient is transfused immediately after operation.

2. This woman, aged 56, was in good general health. The lesion was local without metastases or extension. During the mobilization of the bowel from the sacrum, the lateral sacral vessels were injured. They retracted into the sacral foramina. She died on the operating table from hemorrhage and shock.

3. This woman, aged 59, was obese but her health and physical condition were consistent with her age and weight. Determination of the point for ligation of the vessels was difficult. The remaining anastomotic circulation was inadequate. The bowel sloughed followed by local infection and peritonitis. She died of terminal bronchopneumonia on the fifth postoperative day.

4. The patient, aged 66 was debilitated. She had asthma, chronic bronchitis and chronic myocarditis. The lesion was operable. The operation was not difficult. She left the operating room in good condition. She died on the fourth postoperative day from a myocardial failure. The importance of a recent cold and sinus infection had been overlooked.

5. An obese woman, aged 51, had severe diabetes, hyperthyroidism and arterial hypertension (190/110). The carcinoma arising in the rectosigmoid had perforated the wall and extended into the uterus. An abscess had formed at the site of the perforation. An abdominoperineal resection with hysterectomy was performed. Wound infection and cellulitis of the buttock developed. She died of cerebral thrombosis on the twelfth postoperative day.

6. A feeble woman, aged 71, had an advanced carcinoma of the rectosigmoid with extensive metastases to the aortic glands. She had partial obstruction which was somewhat relieved following x-ray therapy. At operation, the growth was fixed to the pelvic wall. A cecostomy would have been better judgment. An abdominoperineal resection was done. Following operation, she apparently realized the nature of the condition and refused to eat. She was given repeated transfusions and intravenous feedings. She died on the sixtieth postoperative day.

In reviewing these postoperative deaths, four were deemed preventable. Profiting by the experience gained in these, similar instances should not occur. The last two were inoperable and should not have been done. Without operation, there is little to offer. Other cases with extensive metastases in the liver and the aortic glands have been relieved by resection and the family pleased with the added comfort and length of life. It is important to determine how far the limits of operability can be extended. This attitude, however, will not improve mortality statistics. In this series the operative mortality is 15 per cent.

Curability is difficult to summarize. Without separating the palliative operations, among all the patients operated, 7 out of 11 (63.6 per cent) lived five years or longer; 11 out of 17 (64.8 per cent) lived four years or longer, and 12 out of 20 (60.0 per cent) lived three years or longer. Operability was 95 per cent.

Wilson, Henry: Psychogenic Headache, Lancet **1**: 367, 1938.

Seventy-five patients in whom pain in the head was a prominent symptom were studied. These included 39 women and 36 men in all of whom a physical examination had revealed no disease.

No type of pain was found characteristic of the psychogenic headache. The onset is frequently forgotten and is often the result of an evolutionary process beginning as a headache of simple worry.

Psychogenic headaches may be classified as follows:

Type 1. Headaches accompanying simple worry, readily recognized by patients as due to disquiet about current concerns.

Type 2. Headaches incidental to anxiety states, in which cardiac, gastric, or other symptoms are prominent.

Type 3. Chronic headaches, often of the pressure type, occurring especially in rigid individuals who show signs of emotional immaturity.

Type 4. Headaches conforming to description of hysterical pains, in that a single symptom is present without signs of anxiety or obsessional conditions, but in which a history reveals that the headache has been a substitute for these, or in which its disappearance is followed by the emergence of anxiety conditions.

Type 5. True hysterical headaches, not preceded by other neurotic conditions.

In the first two types the prognosis is best but depends largely upon the flexibility of the personality. Out-patient therapy consists in obtaining an adequate history, discussing environmental strains, and reviewing the patient's capacity for adjustment.

CARL P. HUBER.

FURTHER OBSERVATIONS ON THE ROLE OF STREPTOCOCCUS IN SO-CALLED TRICHOMONAS VAGINALIS VAGINITIS*

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IT IS our purpose in this paper to establish further the significance of a specific strain of streptococcus as the causative factor in so-called *Trichomonas vaginalis* vaginitis. This work is a continuance of that done by one of us (G. F. H.) in 1932. The clinical material was obtained from the Departments of Obstetrics, Gynecology and Bacteriology of the University of Illinois College of Medicine, and from private practice. All bacteriologic investigations were carefully performed and controlled under the direction of Prof. Lloyd Arnold, of the Department of Bacteriology of the University of Illinois College of Medicine.

A survey of the literature clearly shows that the role of the *Trichomonas vaginalis* in acute inflammatory conditions of the vagina has not scientifically been determined. This conflict of opinion has existed ever since the parasite was first discovered by Donné in 1837. Scanzoni in 1856 was the first to attempt to establish its pathogenicity and to discuss the symptoms and treatment of the condition. He was followed in later years by Massa in 1885, Marchand, 1894, N. S. Davis, 1896, Mazzanti, 1900, Brumpt, 1913, Hoehne, 1916, and others, all of whom attempted to further the work of Donné. DeLee in 1918 was really the first clinician to emphasize the significance of the trichomonad and undoubtedly stimulated the more recent group of workers in this field, among whom are Bland, C. H. Davis, Stein and Cope, Cornell, Goodman, Karnaky, Furniss, Rowlett, and others. These men have tried not only to verify the work of the early observers but also have concentrated upon the treatment of this condition. In spite of the careful work done in this regard, the problem is far from solved. However, the literature is by no means lacking in work done to question the pathogenicity of the trichomonad, and the recent work of Hesseltine, Plass and Borts, Adair, Allen and Jenson, Jacoby and Der Brucke, Hibbert and others, clearly demonstrates both in the laboratory and clinic that there may be other causative agents working either independently of the parasite causing the disease or in symbiosis. Craig and Faust in their recent publication of 1937 make the following statement regarding the pathogenicity of the trichomonad—"Although the *Trichomonas vaginalis* is usually found in an abnormal vagina, and while gynecologists almost universally regard a form of vaginitis as being caused by the organism, there is no evidence of scientific value demonstrating that it is a pathogenic parasite. On the other hand there is much experimental evidence proving that it is harmless and incapable of causing any pathologic lesions. Dobell in 1926 was able repeatedly to infect the vagina of monkeys with the parasite from women without any lesions of inflammatory reaction resulting, and concluded that it is not pathogenic to normal hosts. Whether it may aggravate an already existing inflammatory condition of the vaginal tract is undecided, but it must be ad-

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mitted that there is not sufficient evidence to prove that it is pathogenic of itself." This work has as yet not been verified, and therefore we consider the results inconclusive at this time.

To us, the confusion in the minds of the gynecologists regarding the disease is evidenced by the diversity of remedial agents advocated in its treatment. These vary from douches of all colors and concentrations, powders, vaginal suppositories, and tablets, to ointments, tampons and packs.

It has repeatedly been shown by many observers that the trichomonad may be present for long periods of time in the vaginal secretion without producing symptoms, and we have at the present time under observation 19 patients, all of whom have harbored the parasite for periods ranging from five months to a year and show no clinical evidence of a vaginitis, and in whom repeated smears fail to show the streptococcus in question. Likewise, it has been definitely proved by us and others that the trichomonad can still be found in the vaginal secretion after the patient has been rendered symptom-free by our own method of treatment or by any of the numerous other methods advocated today. Also, we have repeatedly seen cases having all the clinical manifestations of so-called *Trichomonas vaginalis* vaginitis which fail repeatedly to reveal the presence of the parasite in the discharge, postmenstrual or at other times. To us, at least three possible explanations suggest themselves concerning the clinical observations so far made by the workers in this field: (1) an independent causative agent other than the trichomonad may produce this clinical syndrome; (2) the symbiotic relationship between the trichomonad and the streptococcus as suggested by others may be the causative factor; (3) the failure of patients harboring the parasite to exhibit clinical manifestations of vaginitis may be due to individual immunity established for one or both of these organisms. In this presentation we shall deal chiefly with the first of these possibilities.

The organism isolated from our cases has been positively identified as the *Streptococcus subacidus* of Holman. From our observations, which check with those of Holman and Bergey, it has the following characteristics: it appears as a slightly elongated small diplococcus, noncapsulated, and develops short chains on blood agar or in broth. In the sugar media it ferments dextrose, saccharose, maltose, levulose and trehalose, while in 13 other sugars no fermentation is produced. The zone of hemolysis on blood-agar plates is narrow and not as definite as in other strains of hemolytic streptococci, and no green coloration was noted. They are gram-positive, and are killed in ten minutes by a temperature of 65° F., which definitely distinguishes them from the *Streptococcus fecalis*. Holman says of them: "They are not common, and the sources would suggest that the majority of the strains are highly pathogenic. They have high invasive power, and attack tissues in a state of low resistance. Clinically, the cases are characterized by a chronic, mild course, with frequent exacerbations."

The established pathogenicity of the *Streptococcus subacidus* was proved in our work by experimental inoculation of 5 patients with a pure culture of the organism. We were successful in 4 of these cases in producing definite vaginal pathology, while in the fifth case no vaginitis was noted. The bacterial flora in all of these cases was studied and all found to be free of the trichomonad and could be classified as normal. Two of these 4 women had suprapubic hysterectomies performed during the preceding year, while the other two were menstruating normally. It was of interest to note that in the latter two cases the vaginitis was more acute, the symptoms more pronounced, and the growth of the implanted streptococcus was much more profuse. Objectively the symptoms produced were intense redness of the cervix, vaginal mucosa and vulva, and a gray-white, sticky discharge. Subjectively the patients all complained of a tenderness, burning and itching about the vaginal orifice, and a whitish discharge that "scalded the parts," as one patient explained.

The inoculation was done by applying an active broth culture to the vagina with a sterile cotton swab, and a wick-like sterile cotton tampon soaked in the culture was allowed to remain in the vagina for twenty-four hours. During the period of observation before treatment was instituted the patients were instructed to refrain from coitus, to use no vaginal douches, and to be extremely careful regarding their personal hygiene and cleansing of the toilet after stool, inasmuch as the condition present was produced by a pathogenic streptococcus. The symptoms were allowed to remain untreated for three weeks in the hysterectomized patients and through one complete menstrual cycle in the other two. The treatment instituted was as follows: At no time was any bactericidal agent applied to the vagina; the vaginal tract was first cleansed of accumulated debris with dry, sterile cotton. Then a sterile cotton tampon saturated with a broth filtrate of the *Streptococcus subacidus* was packed against the cervix and allowed to remain in place for twenty-four hours before removal by the patient. An intradermal injection of a standardized vaccine made from the *Streptococcus subacidus* was also given at this time. The interval between treatments was one week, and the treatments were discontinued during menstruation. All four of these patients were successfully treated and rendered symptom-free in from four to seven treatments. They report to us once a month for smears and observation, and they have absolutely been symptom-free for periods varying from three to six months.

To us, this series, while limited to only four cases, is of great importance, not only in definitely establishing the pathogenicity of the *Streptococcus subacidus,* but also from the clinical experimental standpoint we were able to fulfill Koch's postulates inasmuch as the following was accomplished: (1) the successful inoculation of a normal patient with a pure strain of a known organism, (2) the reproduction of the characteristic pathology in the host, (3) the recovery and re-identification of the organism from the lesion produced, (4) the successful treatment of the patient by the use of a vaccine made from that organism, and in our cases also by the local use of the broth filtrate, and (5)

to demonstrate definitely that the patient has produced a specific antibody against the organism introduced. Up to the present time this has not been done in working with the trichomonad.

To prove that an immunity can be established in experimental animals, a normal mature rabbit was given nine graduated intravenous injections of an active culture of the *Streptococcus subacidus* at three-day intervals. One week following the last injection the animal was bled and the serum collected. Agglutination tests were made at various dilutions, using the rabbit's serum against the isolated strain of streptococcus and definite clumping and agglutination of the organisms was obtained at dilutions up to 1 to 640. Likewise, to prove that the patients under treatment also developed specific antibodies, and that the immunity persisted after the patient was symptom-free, the serum of 15 patients was used against the known strain of organism and agglutination was obtained in several instances up to dilutions of 1 to 800. Three cases gave incomplete agglutination, and in three cases no agglutination was noted.

In the original work done by Hibbert, in 1932, the vaginal application of the broth filtrate was the only treatment instituted. Here of course was the clinical application of Besredka's principle of establishing a local immunity by the stimulation of the reticuloendothelial system through the absorption of the filtrate by the vaginal mucosa. In the series here reported this mode of therapy was further augmented by the repeated intradermal injections of a standardized vaccine prepared from the *Streptococcus subacidus*. The strength of this vaccine was 250,000,000 per c.c. The amount given and the intervals allowed between injec-

TABLE I. CLINICAL MATERIAL

Total number of cases showing clinical picture of trichomonas vaginalis vaginitis	84
Obstetric cases	39
Gynecologic cases	45
Cases where trichomonas was found	67
Cases where no trichomonas was found	17
Cases where streptococcus predominated	79
Cases showing extensive exfoliation and fecal flora	5

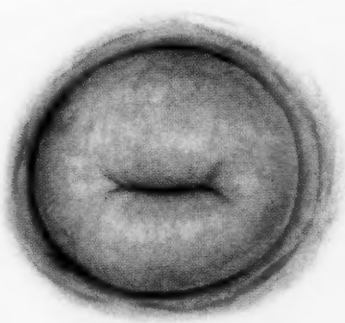
TABLE II. RESULTS OF TREATMENT

Average number of treatments necessary to render patient symptom-free	5
Cases showing exacerbations during treatment	33
Gynecologic cases remaining symptom-free for 3 months	32
Gynecologic cases improved but not symptom-free	13
Obstetric cases remaining symptom-free for three months post partum	31
Obstetric cases having return of symptoms post partum	8
Cases requiring cervical cauterization	17

tions were partially based upon the experience of Corbus* in the work done with the Corbus-Ferry vaccine for gonorrhea. The initial dose was always $\frac{1}{20}$ c.c., the amount increased by $\frac{1}{20}$ c.c. with each injection until the size of the reaction wheal was about the size of a silver dollar or slightly larger. This was obtained in a majority of the cases with

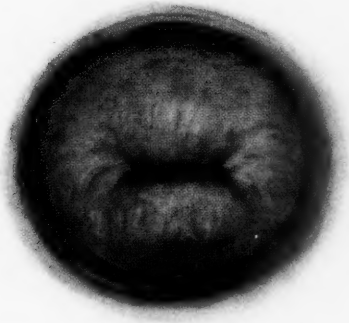
*Personal communication.

ACUTE VAGINITIS PRODUCED BY INOCULATION WITH *STREPTOCOCCUS SUBACIDUS*

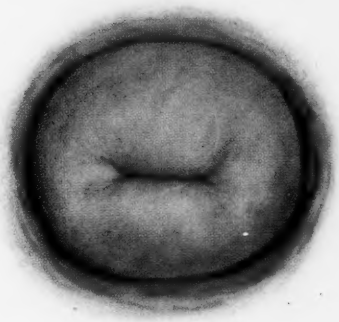


NORMAL VAGINA AND CERVIX
BEFORE INOCULATION

SAME SUBJECT TWO WEEKS
AFTER INOCULATION



AFTER THIRD TREATMENT



AFTER SIXTH TREATMENT

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approximately $\frac{1}{10}$ c.c. dose. It was interesting to note in many instances that as the vaginal symptoms subsided the skin reactions rapidly decreased in intensity and duration, the patient often declaring that the dosage must be smaller because of the mildness of the reaction as compared to that following the first few injections given, when actually the amount given was often $\frac{1}{10}$ c.c. In private practice the injections were given at four-day intervals, and the dosage given usually $\frac{1}{20}$ c.c., seldom increased to $\frac{1}{10}$ c.c. because the patients were more accessible and because it was thought that better results could be obtained by this type of stimulation. However, the results did not differ from those where the treatments were given once a week in the clinic.

A brief outline with special reference to the use of the broth filtrate applied vaginally, and the intradermal injection of the vaccine is as follows:

a. The vagina is wiped free of discharge with dry sterile cotton pledgets.
b. At no time is any solution of germicidal nature used—no green soap nor mucus-liquefying agents.
c. A sterile cotton tampon, approximately the length of the vagina, is saturated with the broth filtrate and inserted vaginally. This is removed by the patient in twenty-four hours. Lamb's wool tampons are unsuitable because they do not absorb and hold the filtrate.
d. The filtrate is applied to the external genitalia where external irritation is noted, and allowed to dry.
e. Intradermal injections of the vaccine are given on the flexor surface of the forearm every four to seven days, the initial dosage being $\frac{1}{20}$ c.c., increasing in amount gradually until the size of the reaction wheal is about two inches in diameter.

A study of the pH concentration of the vaginal discharge in connection with the cases studied was made; bromphenol blue and phenol red were the indicators used. On the whole our observations checked closely with those of Oberst and Plass, Karnaky, Cruickshank and others. In those cases having an associated cervicitis with profuse discharge before treatment, the average pH was 7.0, regardless, in many cases, of the number of trichomonads present. In these cases the bacterial flora was unusually heavy and the streptococcus could usually be found in large numbers, along with staphylococci, gram-positive rods, gram-negative bacilli, pus and debris. After treatment, and especially thermal cauterization of the cervix, the pH sometimes dropped to 4.8. When it did drop, the bacterial flora, particularly the streptococcus, would decrease markedly in numbers, as well as the trichomonad. Agglutination tests made at this time usually showed a definite active immunity established, but this was variable in some cases.

In the cases experimentally inoculated with the *Streptococcus subacidus* the average pH before inoculation was 4.8, and one week after development of the vaginitis the average pH was 6.4, but dropped back again to 4.8, 4.8, 5.0, and 5.0, respectively, as the patients became symptom-free. It was noted that in those cases where the streptococcus was the predominating organism the pH ranged from 6.0 to 7.0, perhaps indicating a more pathologic condition present, if one used the pH of 4.5 as a normal indicator, in contrast to an average pH of 5.5 to 6.5 where the

trichomonads were present in large numbers, but definitely associated with the *Streptococcus subacidus*. Our experience in cases having repeated postmenstrual exacerbations showed that the pH might change rapidly; the reading before the

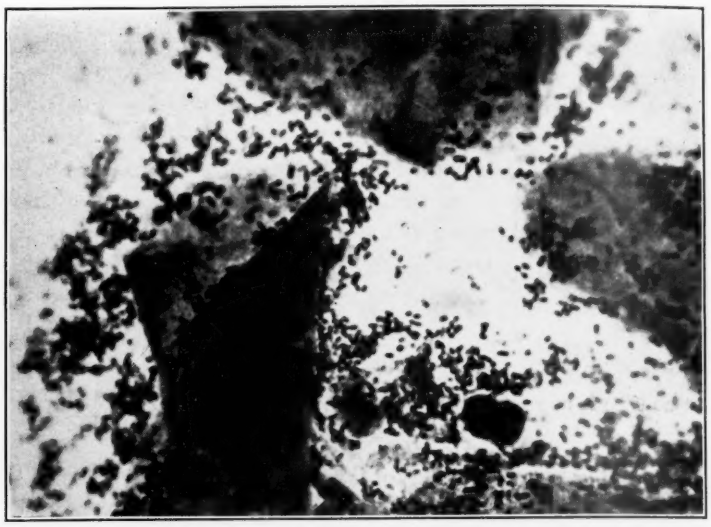

Fig. 1.—(No. 190-446.) Mrs. H., para ii, white woman in sixth month of gestation. Pregnancy was complicated by extreme tenderness of the vagina and vulva, profuse discharge, and itching. *Microscopic examination of discharge:* Few trichomonads were found. Gram stain: many gram-positive diplococci, pus, epithelium and associated flora heavy. Patient treated as described and followed through third month post partum. Symptom-free since ninth month of gestation. Gram stain of vaginal smear at sixth month of gestation, before treatment, showing heavy growth of gram-positive diplococci (*Streptococcus subacidus*), pus cells, epithelium and associated flora.

Fig. 2.—Gram stain of vaginal smear after five treatments in seventh month of gestation. (Note large number of autolized bacteria on plate.)

menstrual period, when the patient was symptom-free, would often be 5.0, and at the height of the flare-up it would be 6.4. A study of the hanging drop in these cases failed to show any appreciable increase in the number of trichomonads, but the Gram stain of the discharge often showed a marked increase in the number of

streptococci as well as the gram-positive and gram-negative bacilli, staphylococci, and pus cells. The average pH in the prenatal cases untreated was 6.8, while that in the gynecologic group was slightly lower, 6.2. In many cases showing very little discharge but a marked redness and extreme tenderness of the vagina, and showing comparatively few trichomonads but a heavy growth of *Streptococcus subacidus*, the initial pH before treatment was from 6.4 to 7.0. After several treatments, which rendered the patient symptom-free for several weeks, the pH was frequently found

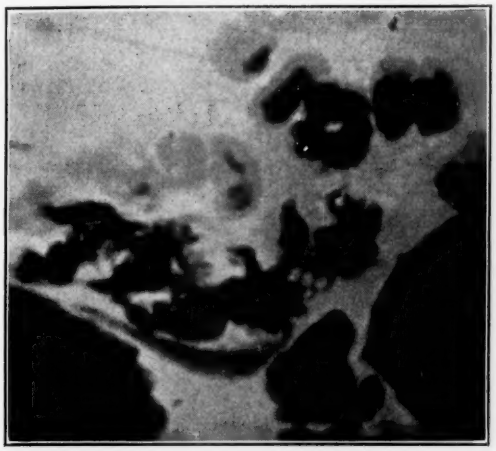

Fig. 3.—Gram stain made in ninth month gestation, showing scant bacterial flora. Patient symptom-free.

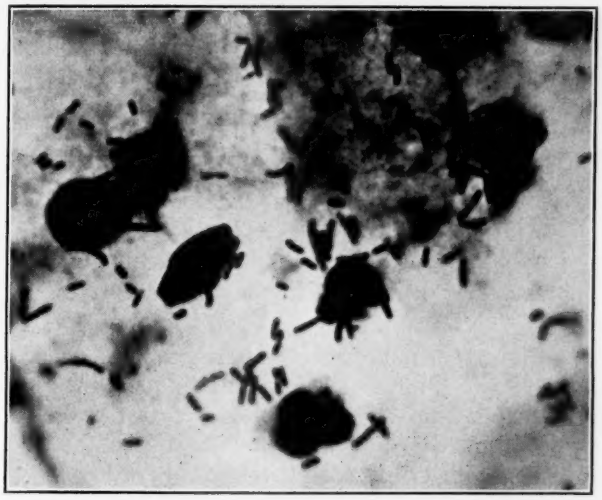

Fig. 4.—Gram stain made at tenth week post partum, showing almost pure growth of Döderlein's bacillus. Patient symptom-free for thirteen weeks.

to be 4.8 to 5.0, at the same time smears from the vagina showing very few streptococci, staphylococci, gram-positive and gram-negative bacilli, many epithelial cells, a few scattered pus cells, and Döderlein's bacilli present, although little change in the number of trichomonads was seen. This would indicate that clearing the vagina of the streptococci may have helped bring the pH nearer to normal and aided the vaginal mucosa in returning to a normal physiologic condition by raising local immunity, regardless of the parasites present. In other words, our observations

led us to believe that the number of trichomonads present in the majority of cases studied does not change in proportion to the change of pH reading as does the growth of the *Streptococcus subacidus*. It might be of interest to know that the pH of the broth before it was inoculated with the *Streptococcus subacidus* was 7.8, and the pH of the broth filtrate as we used it averaged 6.2. Whether the filtrate itself aids in the process of changing the pH of the vagina is undecided.

To clear up adjacent active foci of infection is of great importance, as is brought out by the number of cases having thermal cauterization of the cervix. Freeing the vagina of this copious discharge removes an excellent bacterial medium and aids in the efficiency of the treatment. We also had three instances of chronic Bartholinian abscesses that undoubtedly played a part in causing repeated exacerbations, and one case of an infection of Skene's glands that was destroyed by cautery. In other words, to build up the resistance of the pelvic tissues is of im-

Fig. 5.—Showing *Streptococcus subacidus* from broth medium, showing chain formation.

portance, and removing any factor that prevents an establishing of normal cellular reaction and function plays a part in the treatment of these cases.

Many interesting and puzzling observations were noted in connection with our work. We were by no means successful in rendering all patients symptom-free. Some absolutely failed to respond to our therapy, for no apparent reason. However, it is of great importance to realize that the majority of patients with this type of infection can be rendered symptom-free for months without applying mechanical, thermal, or chemical means to the actual destruction of the parasite.

The possibility of transmission of this disease by coitus to the male was directed to my attention by the following case.

The husband and wife came to one of us (G. F. H.) quite upset because a diagnosis of gonorrhea had been made in both, yet both parties denied exposure. A hanging drop of the vaginal discharge showed a few scattered trichomonads, and a Gram stain of the smear showed a heavy growth of bacteria, including a large number of *Streptococcus subacidus*, staphylococci, many bacilli, and pus. The anterior

urethral smear from the husband showed just a few trichomonads and a corresponding flora with the Gram stain. Prostatic secretions were, as far as could be determined, normal. This man was treated as follows: an anterior urethral injection of the broth filtrate was given twice a day, a bland diet prescribed, and plenty of fluids. In seventy-two hours all the swelling and inflammation and dysurea disappeared, and scarcely enough discharge was present to make a smear. He was symptom-free in four days and has had no recurrences. Sexual continence was advised, to avoid re-infection.

We believe that there are many phases of this work that require more elucidation, and we shall continue to study the problem further in our clinic.

From our observation may we draw the following conclusions:

1. The *Streptococcus subacidus* found in patients presenting the clinical picture of *Trichomonas vaginalis* vaginitis is pathogenic, as shown by its fulfillment of Koch's laws.

2. It produces an immune reaction (agglutination) when injected intradermally.

3. Local clinical improvement was more rapid and apparently more lasting when general antibody reaction was stimulated by the vaccine in addition to the local antibody stimulation by the filtrate.

4. The pH of the vagina was found to be relatively high when there were large numbers of *Streptococci subacidus* present, and to be lower as they disappeared, irrespective of the presence or absence of the trichomonads.

5. The disappearance of the clinical picture and symptoms with the disappearance of the *Streptococcus subacidus*, occurring in the presence of the trichomonads, suggests the former as the chief factor in the production of the lesions.

6. Further efforts to eradicate this streptococcus from the genital tract, and to raise the general immunity to this organism, seem the logical way to attempt the control of this infestation.

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DISCUSSION

DR. FRED L. ADAIR, CHICAGO.—With this contribution Dr. Hibbert and Dr. Falls have proved the pathogenicity of *Streptococcus subacidus* in the causation of various cases of vaginitis. They have proved this especially in its association with trichomonads, but so far as I can see the role of the trichomonad is still undetermined.

When organisms in symbiosis produce a pathologic process we have to remember that any therapy which affects either organism would be likely to result in a cure. Assuming for a hypothesis that trichomonads and other organisms work in symbiosis, we might sometimes see *Streptococcus subacidus* and, in other cases, there might be other organisms. Any therapy which has a destructive effect or diminishes the activity of one of these organisms working in symbiosis would result in a certain percentage of cures.

DR. H. C. HESSELTINE, CHICAGO.—Perhaps some proponent of the idea that the trichomonads are pathogenic will point out that 29 per cent of the gynecologic group were not relieved of symptoms by the therapy employed. Such a criticism is not valid in view of the fact that no single therapeutic measure (in a sufficiently large and adequately controlled series) has removed all symptoms. The contributions by Allen, Jensen and Wood demonstrate definitely the importance of the male urinary tract as a focus for the genital reinfection. Therefore, with this and other sources of reinfection, a minority of failures may be expected. These unsatisfactory cases may well be the result of reinfection rather than a failure of the remedial agent.

In contrast to this specific therapy of Hibbert and Falls, the nonspecific lactose therapy employed at The University of Chicago Clinic in The Chicago Lying-in Hospital enhances the development of a normal bacterial flora. The normal physiologic and biologic state is unfavorable to many pathogenic agents which may attack the vagina. It seems pertinent to ask if Drs. Hibbert and Falls have studied any of the other bacteria associated with the vaginal trichomonads, particularly anaerobic ones, and some of the gram-negative small cocci which are present not infrequently in considerable numbers.

DR. KARL J. KARNAKY, HOUSTON, TEXAS.—I have been doing extensive research on *Trichomonas vaginalis* and leukorrhea for more than six years at the Jefferson Davis Hospital, Houston. I have cultured all bacteria associated with *Trichomonas vaginalis* in all culture media obtainable and inoculated them into 35 women, free of *Trichomonas vaginalis*. In these cases I obtained no itching, and in a few cases only a slight discharge. In no case did I get the typical signs and symptoms of *Trichomonas vaginalis*. But when I inoculated *Trichomonas vaginalis* and the associated organisms together I obtained typical signs and symptoms of itching and burning of the external genitalia.

I have also observed in positive cases of *Trichomonas vaginalis* with pruritus vulvae that as soon as I got rid of the trichomonads the patient became free of her pruritus. Furthermore if one will take smears every day or week, it will be noted that in a case of *Trichomonas vaginalis* which has been cured, as soon as she begins to itch again the trichomonads can be found once more. The clinical symptoms so closely parallel the vaginal smear that I am still more inclined to believe that *Trichomonas vaginalis* is a pathogenic organism.

I have inoculated pure cultures of streptococci from the throat into five normal vaginas and in one case I obtained red superficial blotches, ranging in size from a dime to the size of a half dollar. These were not like the small round discrete spots seen in some cases of *Trichomonas vaginalis*. On the other hand in a series of 4,000 positive cases of *Trichomonas vaginalis*, we failed to find the streptococci any oftener than in the non-trichomonad cases. We are inclined to believe from our clinical observations and trichomonad research that trichomonas is more likely to be the causative organism than the streptococci. Yet I am going to give Dr. Hibbert's vaccine a good trial.

In almost all vaginal infections we have a hypo-acidity. So as the result of the research of Cruickshank and Sharman and of myself, I began about four years ago to use glucose, maltose, lactose and saccharose, because they are the sugars broken down by Döderlein's bacilli, in the treatment of vaginal leucorrheas. In America I was the first to use sugars in the treatment of *Trichomonas vaginalis*, and this I presented in an exhibit before the American Medical Association in Atlantic City two years ago, in Texas, and elsewhere. Since my first work on the use of sugars in the treatment of *Trichomonas vaginalis*, others have made similar reports.

The more mixed is the bacterial flora, the more the pH approaches the alkaline side, the fewer Döderlein bacilli are present, the less sugar is found in the epithelial cells, and the lower is the height of the mucous membrane.

We are using glucose-lactose tablet, pH 3.0-3.3, containing 1½ gr. of 5-7 diiodide-8-hydroxyquinoline. We have increased our cures, by from 10 to 15 per cent, by the addition of acids to our sugars used.

One must clear up any associated cervical infection because the highly alkaline cervical discharge (pH 8.0-9.0) neutralizes the acid of the vagina and so lowers the resistance of the vagina. We treat the patient with glucose-lactose tablets (pH 3.0-3.3) for twelve days followed by the use of vinegar douches (3 tablespoonsful to 2 quarts of tap water) and then cauterize, coagulate or cone the cervix.

I have found many cases of *Trichomonas vaginalis* with the organisms in the prostate, under the prepuce, and in the urethra of men. I have seen a convict who has been in jail for a year with trichomonads in his prostate. I now believe we cure almost all cases of *Trichomonas vaginalis*, and the small percentage that we are unable to cure are re-infections from the sexual partner.

DR. HIBBERT (closing).—It has been a question, as to what type of treatment will restore the tissues to their normal condition. I have proved definitely in my work that that can be done by nothing more than an application of a streptococcic filtrate. To apply different medicaments to the vaginal mucosa and to dry up the vaginal tract is not helping nature to restore normal conditions in that vaginal tract. In these cases I used no medicaments but I was able to get the patients symptom-free and to restore the bacterial flora, as well as the pH concentration, to normal.

Tenney, Benj. Jr., and Parker, Fred. Jr.: Significance of the Weakly Positive Aschheim-Zondek Test, New England J. Med. **218:** 561, 1938.

Sixty cases that showed a weakly positive Aschheim-Zondek reaction were followed up to a definite diagnosis. The majority of these patients miscarried. In a relatively large number a tubal pregnancy was found at operation. No patient had a normal pregnancy, four patients were not pregnant.

The authors conclude that a weak positive reaction after the first few weeks of pregnancy indicates some abnormality; in the presence of signs of a threatening abortion it indicates a poor prognosis. Tubal pregnancy must always be carefully considered in this type of test. Thus a weakly positive Aschheim test may be of as much value as a positive or negative one.

HUGO EHRENFEST.

Ernst, S.: Estrogenic Substance in Cases of Milk Fistula and Mastitis, Zentralbl. f. Gynak. **61:** 1420, 1937.

In 1936, Lindemann reported the rapid healing of a milk fistula which followed an incision in the breast for mastitis by administering estrogenic hormone. Ernst reports two successful results with the same therapy. In these cases, rapid cessation of secretion of milk and spectacular healing of the fistulas could not be attributed to anything but the estrogenic substance.

J. P. GREENHILL.

A CONSIDERATION OF ARTIFICIAL FEVER THERAPY AND SULFANILAMIDE THERAPY IN THE TREATMENT OF GONORRHEAL INFECTIONS OF WOMEN*

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(From the Mayo Clinic)

THE treatment of gonorrheal infection of women has undergone a marked change in the past few years. The use of the Elliott vaginal heat regulator and the vaginal application of diathermy have aided considerably in the treatment of gonorrheal infections of the female genital tract by permitting a more efficient application of heat to the pelvic viscera. Recently, artificial fever therapy has been used to treat such infections by elevating the general temperature of the patient; if the elevation of temperature is maintained for a sufficient length of time it will destroy the Neisseria gonorrhoeae. Local heating of the pelvic tissues by one of the two methods previously mentioned has been used in conjunction with artificial fever therapy and has resulted in an improvement in the results together with lessening the number of fever treatments necessary to effect a cure. The technic and the results of treatment with artificial fever therapy have been published in numerous articles. In more than 90 per cent of cases in which female patients have been treated by this method, consistently negative cultures have been obtained on chocolate blood agar. The failures usually may be explained by a strain of Neisseria gonorrhoeae that is heat resistant or by the inability of the patient to tolerate the high temperature necessary for a sufficient length of time. More recently, a further advance has been made in the treatment of gonorrhea by the oral administration of sulfanilamide. Experience in the use of sulfanilamide in the treatment of this infection of the female genital tract is as yet insufficient to permit a final evaluation of the percentage of cures that may be expected. However, conservative consideration of the data so far accumulated indicates that from 80 to 90 per cent of clinical remissions may be expected in cases in which patients are treated by this method.

We wish to report two groups of cases of gonorrheal infection of the genital tract among women. Group 1 consists of cases in which the patients were treated by fever therapy in an attempt to arrest the disease by a single ten-hour fever treatment. Thirty-seven cases are included in this group (two of the patients received the treatment combined with the administration of sulfanilamide). In addition to the usual management of the patient who is receiving a long fever treatment we feel that two factors have contributed much to the successful treatment. The first of

*Read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

these is the exposure of the skin to the ultraviolet lamp for a sufficient length of time to produce a mild erythema followed by immersion in the Hubbard tank for thirty minutes and wrapping in blankets for one and one-half hours. The vasodilatation thus secured aids the patient in tolerating the prolonged fever treatment. The second factor is the intravenous injection of a 5 per cent solution of dextrose in physiologic saline solution immediately following the treatment. In those cases in which the value for the systolic blood pressure drops below 80 mm. of mercury, the intravenous injection should be commenced at once before completion of the fever treatment. This prevents the danger of circulatory collapse. All of these 37 patients in Group 1 received treatment with ultraviolet lamp and immersion in the Hubbard tank preliminary to the sessions in the fever cabinet. Thirty-one of the 37 patients received a single ten-hour treatment in the artificial fever cabinet at a temperature of more than 106° F. Twenty-two of the 31 patients who received a single ten-hour treatment received additional local heating with either the Elliott vaginal heat regulator or vaginal diathermy. In 9 cases local application of heat was not employed. Five patients were unable to tolerate the ten-hour treatment at the first attempt but were able to do so at the second treatment. Thus, 31 patients of the 37 patients received a single ten-hour session in the fever cabinet. In 29 (93.5 per cent) of these cases cultures made from the urethra and cervix on chocolate blood agar, were consistently negative. Six of the 37 patients were given multiple artificial fever treatments. Two of these received two treatments at the time we were instituting the single long fever treatments; one patient who had a severe gonorrheal arthritis received two long treatments in addition to sulfanilamide, chiefly because of the arthritis; one patient was treated three times before the cultures became consistently negative; one patient who was fifty-eight years of age and who had not responded to adequate doses of sulfanilamide was given two short treatments of five and six hours after which we obtained consistently negative cultures. One patient received four treatments in the fever cabinet; in two of the treatments additional heat also was applied locally. In spite of this treatment the cultures remained consistently positive. She was later treated with sulfanilamide when this drug became available; the cultures then remained consistently negative for the Neisseria gonorrhoeae. Table I is an outline of the treatment in this case. Thus, 34 (94.1 per cent) of the 37 patients treated with fever therapy were found to have consistently negative cultures following treatment. In two cases it was necessary to administer sulfanilamide in combination with the fever therapy before consistently negative cultures were obtained. In the case illustrated in Table I the results of fever therapy were considered unsatisfactory. In this instance sulfanilamide was not administered in combination with the fever therapy but was given later.

Group 2 consists of cases in which the patients were treated with sulfanilamide. The oral administration of sulfanilamide has been found to give satisfactory results as it is readily absorbed from the gastrointestinal tract. The drug is excreted almost entirely through the kidneys. In the event of an untoward effect the administration of large amounts of fluid

will quickly eliminate the drug from the body. In our experience the drug has been well tolerated by the majority of patients. Nausea may occur and vomiting occasionally is experienced. Headache, generalized aching, dizziness, and, at times, paresthesias are noted. Some patients have a sense of euphoria. In one case the patient experienced a rather pronounced febrile reaction. In this case the drug was allowed to dis-

TABLE I. A CASE IN WHICH ARTIFICIAL FEVER THERAPY FAILED TO CURE A GONORRHEAL INFECTION BUT IN WHICH SUBSEQUENT ADMINISTRATION OF SULFANILAMIDE RESULTED IN CURE

DATE, 1937	CHOCOLATE BLOOD AGAR CULTURES	FEVER THERAPY		VAGINAL DIATHERMY		SULFANILAMIDE GRAINS	LOCAL TREATMENT
		HOURS	DEGREES F.	HOURS	MINUTES		
3/22	Positive						
3/24		10	106+				
3/29	Positive						
3/31		10	106+				
4/ 3	Positive						
4/ 6		10	106+	2	40		
4/ 8	Negative						
4/ 9	Negative						
4/14	Positive						Begun
4/16	Positive						
4/27	Positive						
5/11	Positive						
5/13		11	106	6	15		
5/19	Positive						
5/31							Discontinued
6/ 1						40	
6/ 2						60	
6/ 3						60	
6/ 4						40	
6/ 5						40	
6/ 9	Negative						
6/12	Negative						
6/14	Negative						
6/24	Negative						

appear from the blood. Subsequently, a dose of 50 gr. (3.2 gm.) was given subcutaneously and this was followed by a rise in temperature to 103° F. The patient to whom sulfanilamide is given may assume a slate color and at times may have a true cyanosis. Some of the patients who have had these color reactions have had demonstrable amounts of methemoglobin in the blood and sulphemoglobinemia rarely may be found. In a small percentage of cases a reduction in the number of erythrocytes and leukocytes may be noted. It is possible that any of these symptoms might become severe enough to warrant cessation of treatment. In our experience it has been advisable to discontinue the administration of the drug for a time in a few cases but the patients subsequently were able to resume the medication and complete an adequate course of treatment. One no doubt will encounter patients who will not be able to take sulfanilamide but the number of such patients will likely be small. This drug should be administered only under the direction of the physician who prescribes it and who will assume the responsibility for observation of

the patient during the duration of the treatment. A marked anemia or a renal insufficiency may be a contraindication to the use of sulfanilamide. During the course of treatment it is advisable to repeat the examination of the blood from time to time in order to be sure that a significant anemia does not develop. A slight drop in the value for the hemoglobin and in the number of erythrocytes and leukocytes is not infrequently seen but is not a contraindication to continuing the treatment.

The dose of sulfanilamide varies in the experience of different physicians and also depends on the condition for which it is used. The dose of sulfanilamide employed by us and outlined in this paper has seemed adequate for the treatment of gonorrheal infections. Treatment is commenced by the administration of 60 gr. (4 gm.) of sulfanilamide on the first day; this is divided into four doses of 15 gr. (1 gm.) each. On the second and third days 80 gr. (5.3 gm.) are administered in four doses of 20 gr. (1.3 gm.) each. Beginning on the fourth day a daily dose of 40 to 60 gr. (2.6 to 4 gm.) is resumed. At the end of a week of treatment cultures are taken from the uterine cervix and urethra. If the cultures are negative, administration of the drug is continued and the cultures are repeated in two or three days. If they again are negative, administration of the drug is discontinued. Repeated cultures are then taken until four negative cultures have been obtained. One of these must be obtained immediately following the cessation of menstruation. If at the end of a week of treatment the cultures still are positive, the treatment should be continued. Should infection still be evident in the cultures at this time it is well to ascertain the concentration of the drug in the blood. If this concentration is found to be below 6 to 9 mg. per 100 c.c., the dose of sulfanilamide is probably insufficient and will need to be increased. It is difficult at this time to state definitely how long treatment with sulfanilamide should be continued in the face of consistently positive cultures. The case illustrated in Table II reveals that a sufficient concentration may be maintained for seventeen days and still be ineffective. One must consider the fact that a higher concentration may be necessary for certain strains of Neisseria gonorrhoeae and therefore larger doses may be necessary in some cases.

Sixteen patients were treated by oral administration of sulfanilamide. One patient had failed to respond to adequate fever therapy. Fifteen (93.7 per cent) of these had consistently negative chocolate blood agar cultures after treatment. In one case it was necessary to administer two short sessions of fever before negative cultures were obtained. In this case the concentration of the drug in the blood was higher and the duration of treatment was longer than in the cases in which the cultures became negative. The average duration of treatment as shown in Table III was 10.5 days; the longest course of treatment was twenty-three days and the shortest five days.

The average amount of drug administered was 590 gr. (39.3 gm.), the greatest amount was 1350 gr. (90 gm.) and the least amount was 250 gr. (16.6 gm.). An average daily dose of more than 54 gr. (3.5 gm.) was used.

TABLE II. A CASE IN WHICH THE ORAL ADMINISTRATION OF SULFANILAMIDE FAILED TO CURE A GONORRHEAL INFECTION BUT IN WHICH SUBSEQUENT FEVER THERAPY RESULTED IN CURE

DATE, 1937	SULFANILAMIDE, GR.	CONCENTRATION OF SULFANILAMIDE, MG. PER 100 C.C. BLOOD	CONCENTRATION OF SULFANILAMIDE, MG. PER 100 C.C. URINE	METHEMOGLOBIN: + = PRESENT	HEMOGLOBIN, GM. PER 100 C.C.	ERYTHROCYTES, PER C. MM. OF BLOOD*	LEUCOCYTES, PER C. MM.	SEDIMENTATION RATE, MM. IN ONE HOUR	CHOCOLATE BLOOD AGAR CULTURES	FEVER THERAPY	
										HOURS	DEGREES F.
7/ 6	60							76	Positive		
7/ 7	20		36.5†								
			27.8‡								
7/ 8	50		100.0†								
			66.6‡		13.5	3.89	6,900				
7/ 9	60			+							
7/10	60					4.38	7,400				
7/11	60	8.8	77.0†								
			23.0‡								
7/12	20		222.0†			4.27	7,000				
			177.0‡								
7/13	0								Positive		
7/14	0							44			
7/15	0	Negative		+							
7/16	20										
7/17	0										
7/18	0										
7/19	20	1.8	24.0†								
			26.0‡								
7/20	40										
7/21	40								Positive		
7/22	50										
7/23	50										
7/24	50										
7/25	60								Positive		
7/26	60	8.0									
7/27	70										
7/28	70										
7/29	70										
7/30	30	9.6							Positive		
7/31	10			+							
8/ 1	0										
8/ 2	0				13.65	4.22	14,000			5	106+
8/ 3	40	3.1			9.35	3.11	4,600				
8/ 4	40				11.4	3.39	6,500		Positive		
8/ 5	0									6	106+
8/ 6	40			Trace	9.4	2.88	4,700	18			
8/ 7	40	4.4			9.47	2.72	5,500		Negative		
8/ 8	40										
8/ 9	40										
8/10	40							13			
8/11	40										
8/12	40										
8/13	40										
8/14	40								Negative		
8/15	40										
8/16	30										
8/17	0			Negative	9.75	3.53	5,300				
8/18									Negative		
8/19									Negative		

*Expressed in millions. †Free. ‡Conjugated.

This group of cases is small but would seem to indicate that the percentage of patients who will have consistently negative cultures is essentially the same after sulfanilamide is employed in the treatment of gonorrheal infection as it is after fever therapy is employed. In other words, there are certain cases in which the infection will fail to respond to the administration of sulfanilamide. In this small percentage of cases a combination of fever therapy and sulfanilamide will probably result in consistently negative cultures.

TABLE III. OUTLINE AND RESULTS OF SULFANILAMIDE THERAPY IN SIXTEEN CASES

CASE	DURATION OF TREATMENT, DAYS	SULFANILAMIDE			NUMBER OF NEGATIVE CULTURES	DURATION OF FOLLOW-UP STUDY, DAYS
		TOTAL AMOUNT, GR.	AVERAGE DAILY DOSE, GR.	MG. PER 100 C.C. OF BLOOD		
1	23	1260	60	6.6	4	21
2	14	900	63+	6.1	4	21
3	11	700	63+	6.6	4	28
4	6	310	50+	6.8	4	60
5	8	430	53	6.0	4	21
6	8	430	53	6.6	4	23
7	8	400	50		5	28
8	5	250	50		4	21
9	9	450	50		2	30
10	7	280	40		3	28
11	8	520	65		2	28
12	8	430	53		4	21
13	8	430	53		4	28
14	17	880	50+		5	35
15	8	430	53		4	24
16	21	1350	64+	9.6	*	
Average	10.5	590	54+			

*Culture still positive.

It would seem from our experience that gonorrheal infections of the female genital tract should first be treated by the administration of sulfanilamide if this drug can be given under the direction of the physician. Our experience so far indicates that a large percentage of patients with gonorrhea will respond to sulfanilamide therapy alone. Certain infections will be found to be intractable to this method of treatment. When this is the case it would seem best to recommend a combination treatment with sulfanilamide and artificial fever therapy.

DISCUSSION

DR. CHARLES DRABKIN, ST. LOUIS, MO.—The value of fever therapy in certain diseases has been definitely established. We cannot emphasize too strongly, however, the importance of the preliminary training of the medical and nursing staffs, and the care and caution to be given to the patient before, during, and after the course of treatment. The type of machine used is not as important as the personnel operating the machine and watching the patient. This form of therapy is not adaptable to office practice. Every patient must undergo careful preliminary studies. The same contraindications exist as would make her unfit for a major surgical operation. Patients with heart disease, arteriosclerosis, hypertension, nephritis, diabetes, and tuberculosis are bad risks.

The actual mechanism of fever therapy has not been definitely established. The fever destroys the gonococcus, which is thermo-labile, but the human body tolerates with safety this artificial fever. At the present time, at the Washington University School of Medicine, experiments are being made to determine whether we are dealing with an immune body reaction, rather than merely with a gonococcidal effect. It would seem that all immune substances which can be measured are actually increased during each session of fever therapy. Eventually, practically all patients get well, and the gonococcus is no longer found in smears or cultures at the end of the course of treatment.

At the Barnes Hospital, from Oct. 7, 1935, until Oct. 5, 1937, 211 patients have received approximately 1100 treatments. Out of this number, 21 were women who had an active gonococcal pelvic infection and an acute or chronic inflammatory gonorrheal complication. The Kettering Hypertherm has been used almost entirely for the development of the fever. Of these 21 women, none showed untoward results of any kind, and all have become free of organisms on repeated examinations. In acute cases, the tubal masses showed either definite improvement or complete resolution. In the chronic cases, the adnexal tenderness and induration has markedly diminished or disappeared entirely.

These patients received an average of 4.6 fever treatments of four to five hours each, at temperatures maintained at 106 to 107° F. The interval between treatments was two days. In all but two patients, organisms were not found after the third or fourth treatment, after which an additional treatment was given. Two patients received six and seven treatments, respectively, without disappearance of the organisms. These were tentatively considered as fever therapy failures. However, subsequent follow-up has shown that these cases became free of organisms, when they were examined after their second and third subsequent menses, and have been free of organisms and have remained asymptomatic since.

In one case, the treatment was ceased before completion of the course, because during the induction of the fever, the patient developed repeated attacks of tetany which were refractory to all types of treatment. However, it must be stated that she was then given short-wave therapy to the pelvis. Despite this inadequate course of treatment, the organisms disappeared.

The average age incidence of these patients was 23.6 years. They all showed a definite gain in weight at the conclusion of the course of treatment. Two of the patients were subsequently reinfected by their husbands, which means that the mate must be adequately treated, if we are to establish a permanent cure. One patient who had bilateral salpingo-oophoritis prior to the onset of treatment, subsequently conceived and delivered a living normal infant. This last observation has also been made by Stafford and Warren, who have had complaints from some prostitutes, who had been sterile, but following the completed treatments of fever therapy managed to become pregnant.

We have had no experience in the use of sulfanilamide in combination with fever therapy. However, since the advent of this drug, complications due to the gonococcus have apparently been reduced, as is evidenced by the diminution in the number of patients, male or female, who have entered the hospital for the treatment of acute complications due to the gonococcus.

DR. JOHN F. KUHN, OKLAHOMA CITY, OKLA.—Sulfanilamide undoubtedly is curing and aiding in the cure of a very great number of infected persons. In this paper by Randall, Krusen and Bannick, 15 patients out of a total of 16 are reported cured, and when we consider the simplicity of its administration, we may well hope that this is the answer to our long search. Yet it is unfortunate that the drug has been exploited to the poorly informed lay-public, for it may be a very dangerous drug in lay hands.

Various strains of gonococci will probably require varying blood concentrations. Fortunately a concentration up to 9 or 10 mg. per 100 c.c. of blood will cure a very high percentage of the cases, but some more resistant strains may require much higher concentrations with resultant formation of methemoglobinemia or the causation of the grave agranulocytosis. Wendell of the Department of Biological Chem-

istry and Internal Medicine of Washington University will shortly publish details of experiments dealing with intravenous methylene blue given to overcome methemoglobinemia produced by high concentration up to and above 50 mg. per 100 c.c. of blood. He has definitely proved its value and so we may overcome one of the grave dangers.

Agranulocytosis has been reported following administration of sulfanilamide. Other causative factors have, however, not been ruled out in these cases and there is still doubt as to whether it has resulted from the administration of sulfanilamide. *However, it bears watching.* Visual field defects reported have cleared up after the withdrawal of the drug.

Some complementary treatment may be necessary with the sulphanilamide therapy. Hyperpyrexia may be used when there is available a well organized team to supervise the patient and the apparatus employed. Diathermy or short wave applied and observed by an experienced operator may be worth while, but our results have been disappointing. Heat as applied by the Elliott machine has been worse than disappointing in our hands. The manipulation required of the infected tissues at such frequent intervals is certainly contrary to physiologic processes. We have discarded this method entirely. The simplest form of complementary treatment, the retention of hot normal saline enemata, has given us the best results.

DR. EARL C. SAGE, OMAHA, NEB.—Dr. A. E. Bennett and his associates at the Clarkson Hospital have treated 61 female patients in the Kettering fever cabinet, with an adequate follow-up in 54. Of these patients 19 had positive smears after treatment, and of these 19, nine had had four or more fever treatments. In other words, 17 per cent of those treated had persistently positive smears despite fairly adequate treatment. Treatments were given every third or fourth day and each treatment was of six hours' duration, at 106 or 107° F.

There were 16 women with gonorrheal arthritis, 9 of whom received complete relief, and 7 marked relief. Eleven of these arthritic patients had genital tract involvement as well, and are therefore included in the previous group. That relief of gonococcic arthritis is not inconsistent with the persistence of a genital tract infection is shown by the fact, that 5 of these 11 patients had positive smears after their arthritis had been relieved by fever therapy.

Since, in spite of the time, expense and discomfort involved in taking several six-hour fever treatments, the results were unsatisfactory in 17 per cent of the cases, these workers have recently been trying to clear up gonococcic infections with one ten-hour treatment. The results promise to be at least as satisfactory as with the old technic of repeated shorter treatments, while at the same time much less expensive and more saisfactory for the patient.

DR. RALPH LUIKART, OMAHA, NEB.—Some thermal and chemical tests have been made on cultures in vitro to determine the amount of heat needed to kill the invading bacteria. These tests seemed to be of great value. We found in some that a temperature of 110° F. was required in order to destroy the organisms. Cases that required, as the cultures showed, either a high concentration of sulfanilamide or a high temperature were given different types of treatment.

DR. FRED L. ADAIR, CHICAGO.—It seems to me a priori that infections that are accompanied by high fever reactions in the human body might be the type of infection that would respond to hyperthermia, whereas the type of infection that has a low fever reaction might not respond as favorably to high fever therapy.

The so-called Elliott treatment or local hyperthermia is a valuable method of treating local genital infections in the female. We have used two types of apparatus, one in which the treatment is administered through a hydrostatic bag and another through a superheated air bag. We have treated about 300 cases, and in 90 per cent we have had subjective cures. In a much smaller percentage of cases we have had anatomic cures.

Since starting this treatment three years ago we have followed the patients rather conscientiously for one to seven months. An interesting side light was that we found

that we are not so expert in our clinical differentiation between endometriosis and inflammatory conditions of the genitalia. There was a group of cases which did not respond to this treatment that have come to operation. In 85 to 90 per cent there have not been straight inflammatory cases, but were either endometriosis or inflammatory conditions associated with endometriosis. Hence this method of treatment has come to be regarded not only as of definite therapeutic value but of diagnostic use also.

DR. HOWARD HEWITT, CHATTANOOGA, TENN.—Sulfanilamide may cause an anemia due to the fact that it may not be completely oxidized. My experience with sulfanilamide has been very disappointing. I think from now on I am going to use the intravenous method.

DR. GEORGE E. COWLES, WICHITA, KAN.—I have a patient in the hospital at the present time who, following standard doses of sulphanilamide, developed a deficiency of white blood cells to the point where she had a white count of 600. Following that she broke out with skin lesions, so that her skin sloughed from almost the entire body. For three or four days we thought the patient was going to die. This patient has been in the hospital about a month, and now, after repeated blood transfusions, is recovering. It should be emphasized that sulfanilamide is a very dangerous drug.

DR. RANDALL (closing).—Any treatment that will accomplish symptomatic cure in inflammatory disease of the female pelvis is worthy of consideration. Sulfanilamide therapy perhaps still requires further evaluation; nevertheless we cannot ignore the data that have accumulated. The treatment should be administered under the direction of a physician just as carefully as artificial fever therapy.

ARTIFICIAL FEVER THERAPY IN PELVIC INFLAMMATORY DISEASE*

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(From the Department of Fever Therapy, The Grace Hospital)

IT IS the purpose of this report to evaluate the results of fever therapy in the treatment of forty cases of gonococcal pelvic inflammatory disease. A decade of accumulated experience has proved its value and accurate follow-up observations of treated patients attest to its specificity. Clinical responses in this series have been satisfactory and dramatically prompt.

The treatment of gonorrhea in the female has been accomplished by local tissue heating and systemic hyperpyrexia. Gurnee[2] feels that the combination of the Elliott machine with the fever cabinet affords the best results, a fact borne out by the work of Randall and Krusen. He also found that the combination of short-wave diathermy with the heat cabinet is likely to produce vaginal burns and sloughs. However we have found it inadvisable to combine local tissue heating with systemic hyperpyrexia. When vaginal heating is employed, the surrounding tissues are elevated to temperatures nearly approximating that of the vagina, thus preventing accurate rectal temperature recordings. Since the patient is taking iced saline continuously, mouth tem-

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

perature records are not accurate and the danger of superhyperpyrexia is always imminent. On several occasions when the combined method was used, patients appeared to be near vascular collapse although oral temperatures were only 104° F. Upon withdrawing the patient from the cabinet the temperature was found to be above 108° F. To a lesser extent, vaginal burns from vaginal diathermy have produced tissue necrosis and sloughing.

Our experience has been with the heated humidified cabinet previously described.[1] It cannot be too frequently emphasized that the apparatus used for fever production is of relatively minor importance compared to the care and caution that should be used in administering the treatment. An efficient fever therapy department requires a physician trained and interested in the use of fever, consultants in the various specialties alive to its possibilities, well trained nurse technicians and finally the fever apparatus.

Before subjecting a patient to treatment she is studied with the same care and caution she would receive were she a candidate for a major surgical procedure. A complete clinical survey is made and special chest and cardiac examinations are carried out. It is well to exclude from treatment all patients past the age of 45 and all subjects with evidences of cardiovascular incompetence.

On the morning of treatment breakfast is omitted and 1.5 to 3 gr. of sodium pentobarbital are administered orally. The patient is completely disrobed and placed in a preheated fever cabinet, the arrangement being such that the head and neck are in the open. The patient's body is freely accessible through doors in the sides of the cabinet. The patient lies on a comfortable rubber mattress, the body being encased in blankets.

Heat and humidity are supplied by a thermostatically controlled electrical unit. The maximum temperature of the cabinet approximates 130° F. and an atmosphere of 40 to 50 per cent humidity is maintained. The body temperature is raised at the rate of approximately one degree every fifteen minutes until the desired temperature is attained (106° to 107° F.). When 102° F. is reached one-third of a grain of pantopon is usually administered. An ice cap is placed on the head and a fan circulates the air about the head. Iced saline solution amounting to many liters may be consumed during the treatment. Rectal temperature, pulse, respiration, and blood pressure readings are recorded every ten to fifteen minutes. The body temperature is maintained between 106° and 107° F. for five to six continuous hours. The treatments are repeated every three to five days until the desired result is obtained.

Complications occasionally noted are facial herpes, nausea and vomiting, headache and to a lesser extent general erythema and tetany. Impending cardiovascular collapse is indicated by a pulse rate of more than 160 beats per minute, and treatment should be discontinued immediately when this situation arises.

The ages in our series varied from fourteen to fifty, the average being twenty-eight years. This corresponds to the period of the most active sexual life of the female and incidentally is an age which permits strenuous treatment with relative safety. The oldest patient exhibited a concomitant polyarticular periarthritis and arthritis as well as evidence of gonorrheal ophthalmia.

In more than 90 per cent of our patients a history of contact was established, over 80 per cent of them being married. It was definitely established in most instances that infection came from the husband.

Cervical and urethral smears were examined by the gram method and by methylene blue stain. Eighty per cent of our cases showed the presence of gram-negative intracellular diplococci, morphologically Neisseria gonorrhoeae. The older the infection the less frequent was a positive slide obtained. Interestingly enough the methylene blue stain in our hands was as accurate diagnostically as the Gram

method. Cultures were attempted in some cases but reliance on the smear was usually sufficient for diagnosis. All cases included in this series were checked by smears, either obtained by us or by the referring physician. One patient had left lower quadrant pain, tenderness and discharge with negative smears. The husband admitted a specific infection previous to marriage. Consequently, the patient was given a test treatment with improvement. However, relapses recurred after subsequent treatment and laparotomy revealed pseudomyxoma peritonei as the causal factor.

The duration of the infection before the patient sought medical aid varied from two weeks to three years. Interim treatment in some instances consisted of local chemotherapy, intragluteal milk injections or local pelvic heating, while others denied that any form of therapy had been used.

The most frequent complaints noted were bilateral or unilateral lower quadrant pain, tenderness, and vaginal discharge. Constitutional reactions occurred in direct proportion to the recency of the infection and consisted of chills, fever, and leucocytosis.

The stage of infection was classed as acute, subacute, and chronic. The types of infection were urethritis, Bartholinitis, cervicitis and salpingitis. Monoarticular or polyarticular arthritis was the most frequent complicating factor and occurred in 12 per cent of the cases.

RESULTS

Our criteria of cure is predicated on the absence of gonococci as determined by smear as well as the subsidence of symptoms. The ideal treatment for specific pelvic inflammatory disease in women might be postulated as one free from mortality, providing a cure in minimum time, leaving no sequelae, available to every woman regardless of her economic status and one which leaves the reproductive functions unimpaired. While the ideal by no means has been obtained our experience with hyperpyrexia has yielded the following results with 40 cases:

3 patients were cured with one treatment.
25 patients were cured with two treatments.
5 patients were cured with three or more treatments.
7 patients were either unable or unwilling to continue treatment until cure was effected or failure could be determined.

The longest time any patient has been observed has been three years and no patient is reported who has not been carefully examined for a period of three months following treatment. One patient required eight fever sessions before she became bacteriologically cured although she was completely asymptomatic after the third treatment.

Owing to variable factors the number of treatments necessary to effect a cure could only be determined by trial. It has been our policy whenever feasible to administer one additional treatment after the smears became negative as an added precautionary measure.

SUMMARY AND CONCLUSIONS

Fever therapy is a strenuous form of treatment and its application is attended with some risk. It is a hospital procedure and its successful use requires the services of trained personnel.

Complete cure may be expected in upwards of 80 per cent of cases where three or more treatments are administered, providing the body temperature is maintained at 106° to 107° F. for five to six hours per treatment.

The acute stage of the infection is no contraindication to the use of fever therapy. In fact, the more acute the symptoms, the more dramatic will be the result.

Repeated clinical examinations following treatment indicate that the functions of the female reproductive tract are not essentially altered.

Should fever therapy fail to effect a cure the patient could readily undergo any other form of treatment deemed advisable.

The results obtained in treating 40 patients with specific pelvic inflammatory disease by hyperpyrexia, have convinced us of its efficacy and stimulated our interest in its continued application.

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EFFECT OF QUININE UPON AUDITORY NERVE*

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IT HAS been estimated that of the 10,000,000 deaf persons in the United States, 3,000,000 are children.[1] A committee engaged in a statistical study of the children in public schools for the deaf, stated that of 3,334 children studied, 62 per cent were congenitally deaf.[2]

This statement, in years past, would probably have held little or no interest for obstetricians. The medical literature of the world, however, is gradually accumulating evidence which, although not conclusive, may place a great share of the responsibility for this army of defective individuals upon men who care for women during their period of reproductivity. The effect on the fetus of drugs administered to the maternal organism has long been a problem of interest and at present there are three of principal importance, i.e., alcohol, salicylates, and quinine.

This investigation was undertaken for the purpose of determining the histopathologic effect of quinine administered to the fetus in therapeutic doses via the placental circulation.

REVIEW OF LITERATURE

In this review of literature the attempt was not made to cover completely all of the points involved, particularly those which have to do with definitely established facts, for instance the literature is replete with evidence that quinine has a selective

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action upon the eighth nerve. The evidence is also quite conclusive that quinine is carried through the placental circulation and reaches the fetus in high concentrations.[3, 4] Covell has proved that quinine, given to parturient guinea pigs, in poisonous doses, produces demonstrable changes in the auditory apparatus of the offspring.[5]

Great clinical interest has been aroused among the otologists by the publications of H. Marshall Taylor who, in writing upon this subject, made the following statement: "Despite the fact that modern textbooks on otology point out the selective action certain drugs have for the auditory apparatus, otologists have virtually ignored the possible damage to the ear of the fetus which these drugs may cause when administered to the pregnant woman. That quinine, the salicylates and alcohol can have a permanent influence on the auditory nerve and that quinine in particular has a predilection for this nerve are established facts."[1]

In another publication, Taylor reported 5 cases of complete deafness in children three to five years of age whose mothers were given massive doses of quinine during or before parturition for malaria, attempted abortion, or induction of labor.[6]

In a recent study, Heider reported that in the southern states, particularly Florida and Alabama, two and one-half times more deaf children are born in the second half of the year, corresponding to the seasonal prevalence of malaria.

Degenerative changes in the mechanism of the ear, due to quinine, salicylates, and alcohol, have been reported by Wittmarck,[7] Bernard and Daniel[8] and others.

METHOD

These experiments were carried out upon rabbits. A series of twelve animals in all was studied. The first animal was given ½ gr. of quinine bisulphate by mouth each day for ten days, i.e., 5 gr., previous to autopsy. This was done in order to note the effect of massive doses upon the auditory apparatus of the individual animal. The remaining eleven were animals from three different litters; the mother of Animals 2, 3, and 4 receiving 5 gr. of quinine bisulphate; the mother of Animals 5 and 6 receiving 3 gr.; the mother of Animals 7, 8, 9, 10, 11, and 12 receiving 1 gr. This latter was regarded as being the equivalent of the average therapeutic dosage given to parturient women for the purpose of inducing or stimulating labor, i.e., 15 gr. to parturient women, and 1 gr. to an 8 pound animal, or approximately 16 mg. per kilogram of body weight. The Animals 2 and 12 were autopsied at the age of two months.

The drug was administered by mouth in each instance in order to simulate as nearly as possible actual clinical conditions. With each series of animals autopsied, an animal from a control litter was studied. The control animals were bred, reared, and cared for under absolutely identical conditions to those of the experimental animals. This was done in order to rule out any chronic hereditary or environmental disease which might affect the animals in any manner.

TECHNIC

The material of the control animals and Animal 1 consisted of the auditory nerves alone. The rabbits were killed with chloroform and the nerves were removed immediately after death. The material was preserved in formalin, and also in Mueller's solution. The nerves preserved in formalin were stained by the Spielmeyer Method (myelin sheaths) while the tissue preserved in Mueller's solution was stained by the Marchi Method (osmic acid stain of degenerative fat granules).

From Animals 7, 8, 9, 10, 11, and 12 (1 gr. of quinine via the placental circulation), the petrous pyramid was removed immediately after death and the method of Eckert-Moebius (Handbuch der Hals-Nasen and Ohrenkrankheiten) was employed. It consisted of the following procedures: (1) Wittmaak's fluid for fixation: Pot. bichrom. 5 per cent, 50 c.c.; formalin, 10 c.c.; glacial acetic acid, 5 c.c.; Aq. dest. to 100 c.c. The specimens remained three weeks in this fluid. (2) Decalcification: Nitric acid, 5 c.c.; formalin, 5 c.c.; Aq. dest., 100 c.c. The solution was changed every 3 days. The tissue remained three weeks in this decalcifying solution.

(3) 5 per cent Sod. sulphate for twenty-four hours. (4) Running water twenty-four hours. (5) After cutting the petrous bones into three parts, the following osmic acid stain was used, for 8 days: Osmic acid 2 per cent, 5 c.c.; Pot. bichrom. 5 per cent, 5 c.c.; Glac. acetic acid, 1 c.c.; Aq. dest., 10 c.c. (6) Running water for twenty-four hours. (7) Embedding in celloidin: 70 per cent alcahol, 1 day; 95 per cent alcohol, 1 day; Absol. alcohol, 1 day; thin celloidin, 2 weeks; medium celloidin, 4 days; thick celloidin, 2 days.

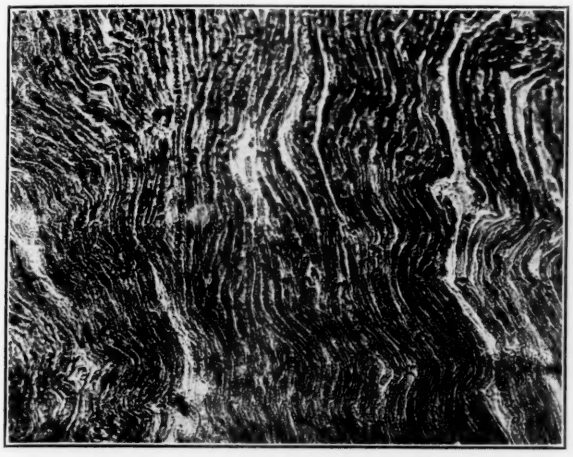

Fig. 1.—Normal auditory nerve. Marchi stain.

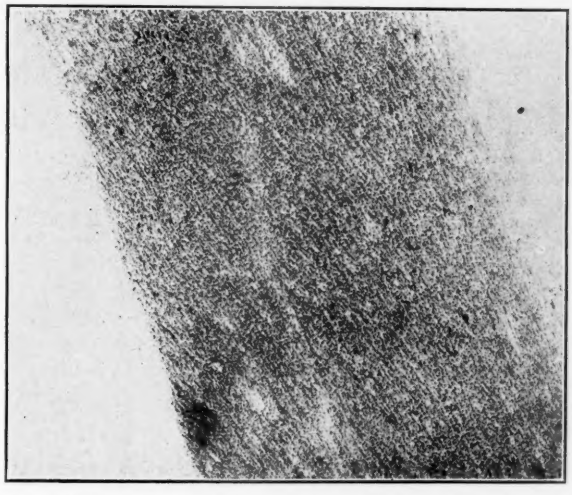

Fig. 2.—Rabbit's auditory nerve after receiving quinine. Marchi stain. Every fiber contains minute black granules of degenerated myelin. (Animal 1.)

DISCUSSION

The auditory nerves in the control animals stained with the Marchi stain show only occasional black granules (Fig. 1). In the material obtained from Animal 1, receiving 5 gr. of quinine bisulphate by direct administration, every fiber contains minute black granules of degenerated fat globules (Fig. 2). Fig. 3 shows the same nerve stained by

the Spielmeyer stain. We see degenerated myelin sheaths appearing as whitish gray spots. In Figs. 4, 5, and 6 we were able to examine the spirale ganglion (Fig. 4), the auditory and vestibular nerve (Fig. 5) and the peripheral neuron of the cochlear nerve (Fig. 6). Please remember that this is material from the important Litter 3; important because this litter received 1 gr. quinine bisulphate in utero, cor-

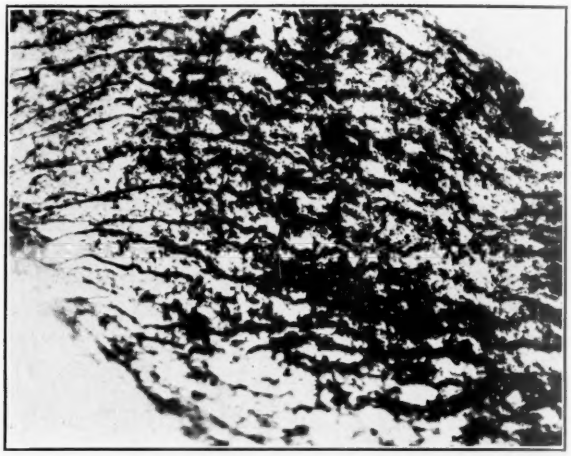

Fig. 3.—Same nerve shown in Fig. 2 stained by Spielmeyer method. Degenerated areas shown as whitish-gray spots.

Fig. 4.—Spirale ganglion from Litter 3. Marchi stain. Many degenerated ganglion cells with fatty globules in the cytoplasm.

responding to the therapeutic dose given ordinarily to parturient women. The spirale ganglion showed marked degenerative changes. Many ganglion cells showed destruction of the nuclear substance, condensation of the cytoplasmic structures, and fatty degeneration of the cytoplasm. There is some round cell infiltration of the stroma of the ganglion. Many cells were shrunken and without definite structure.

In Fig. 5, we see the auditory and the vestibular nerve stained by the Marchi method in which marked degeneration is found in the auditory nerve with a very slight degeneration found in the vestibular nerve. In Fig. 6, we find the cochlea with the organ of Cortii did not show pathologic changes. We did not find any hemorrhages or degenerative changes in the structure as some otologists believe. The periph-

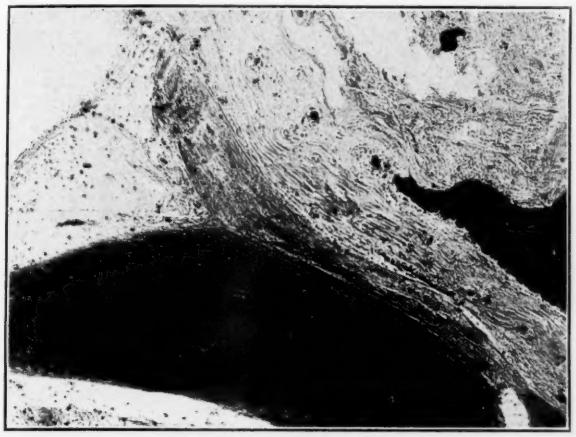

Fig. 5.—Marchi stain of cochlear and vestibular nerve. Black granules of fatty degeneration myelin in lower nerve (cochlear nerve), Litter 3.

Fig. 6.—Peripheral neuron of cochlear nerve. Black granules of osmic acid stained fat in nerve fibers. Litter 3.

eral neuron of the cochlear nerve, however, again showed marked degenerative changes, i.e., fat globules stained with osmic acid.

Whether the lesions in the spirale ganglion are primary and those in the neurons and axons of the cochlear nerve are secondary, is difficult to decide from our histological findings. It seems more likely that the myelinated nerves are affected first by the toxic effect of the

quinine, since the degeneration in the ganglion appears to be less severe than that of the nerve fibers.

SUMMARY

As stated previously, this work was undertaken for the purpose of determining histologically the effect on experimental animals of dosages of quinine bisulphate given in utero corresponding to the dosage received by parturient women for the purpose of inducing or stimulating labor.

These experiments show rather conclusively that small doses of quinine do produce definite destructive changes in animals. The question now naturally arises, what is the inference to be drawn clinically? The otologists are certain that complete deafness is likely to occur in individuals receiving massive doses of quinine in utero. If this is true, are we not justified in assuming that slight degeneratve changes produced by smaller doses might be responsible for a great many of the auditory defects which develop in young or young adult individuals?

Many obstetricians tell us that no untoward effects have been observed in the use of quinine over long periods of years. This statement is open to question, however, because the obstetrician often times loses sight of these patients after a few years, and the hearing defects are not called to his attention or the history of quinine administered during parturition may have been overlooked. Some investigators believe that auditory defects occur only in individuals who have an idiosyncrasy to quinine. This conclusion is not borne out by our experiments because every individual of each litter of animals showed the same degenerative changes in the auditory nerve.

Now we all of course realize the impossibility of drawing definite clinical conclusions from animal experimentation. It would seem, however, that enough evidence is at hand to warrant intensive clinical study by obstetricians as well as otologists. This can best be brought about by a very careful scrutiny of the natal and prenatal history of every individual showing hearing defects, to determine whether or not quinine or other drugs were administered in utero. In the meantime, until conclusive evidence is accumulated to prove or disprove this problem, the author is of the opinion that quinine, the oxytocic value of which has always been problematical,[9] had best be omitted from the obstetric armamentarium because we cannot be certain that we are not bringing about great harm to future generations.

CONCLUSIONS

1. Review of the literature proved that quinine bisulphate has a selective action on the eighth nerve.

2. Strong evidence was found in the literature which tends to prove that quinine, in massive doses, administered in utero produces hearing defects.

3. Quinine bisulphate, administered to individual animals in massive doses produced myelin sheath degeneration of the auditory nerve.

4. This investigation shows that quinine bisulphate, administered in utero in therapeutic doses produces degeneration in the auditory nerve, spirale ganglion, and peripheral neuron.

5. With this evidence at hand, intensive clinical investigation is urged to determine whether or not therapeutic doses of quinine bisulphate, administered clinically, will show the same effects.

I wish to acknowledge the valuable assistance of Dr. C. A. Hellwig, Chief of the Department of Pathology, at St. Francis Hospital, Wichita, Kansas, for the technical work and pathologic reports on this material.

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DISCUSSION

DR. MINNIE L. MAFFETT, DALLAS, TEX.—Such careful studies as those of the essayist, as well as of King, Taylor, and others render the possibility of fetal deafness from quinine one that the obstetrician must take most seriously. Probably all obstetricians are agreed that quinine in the induction of labor, or even for the augmentation of uterine contractions during labor, is of little use. Many other methods now available are certainly more rational and dependable. I, therefore, believe that the use of quinine in the attempted induction of labor should be entirely discontinued as long as it is on trial as an etiological factor in deafness.

The internist or general practitioner, however, has another problem. A severe case of malaria must, after all, receive treatment by some recognized method, quinine, plasmochin, atabrine, etc. While the last two are without effect on the auditory nerve, their toxicity in other directions cannot be overlooked. Regardless of this fact, however, some one of them must, of necessity, be used as treatment for malaria complicating pregnancy.

If quinine is as provocative of congenital deafness as these studies would indicate, one wonders what must have been the frequency of deafness in malaria districts during past years when this disease was much more prevalent than at the present time. It would be of interest if comparative statistics could be made available contrasting the conditions existing in the malarial and nonmalarial sections of the country.

Regardless of Fall's statement that quinine is of low toxicity and that as much as 600 gr. have been given to a patient within twenty-four hours without any disturbance, it is still evident that there is a wide variation in the idiosyncrasy of individual persons to this drug. Inasmuch as the placenta undoubtedly does not serve as a barrier against the transmission of the drug to the fetus it would seem evident that a high threshold of tolerance in the mother is no safeguard to possible damage to the auditory mechanism of the fetus. Deafness may unfortunately not be discovered until the child is of school age.

DR. J. W. REDDOCK, NEW ORLEANS, LA.—In the last few years we have discontinued the use of quinine in the induction of labor. It was my opportunity to carry out a series of inductions using rupture of the membranes in an effort to induce labor without the use of quinine. The results of the induction of labor by this

means have been as satisfactory and probably even more so than when quinine is used. There is rather definite reason to believe that quinine is decidedly damaging to the fetus.

DR. WILLARD R. COOKE, GALVESTON, TEX.—I am able to report three cases of so-called congenital deafness in children whose mothers had quinine for the induction of labor (15 to 30 gr.). Whether this had anything to do with the deafness we do not know. On the other hand, I have had no opportunity to treat malaria, because it does not occur in Galveston. I have seen only three cases of malaria complicating pregnancy, and in two of these the children were perfectly normal in hearing. In one case the mother has estivo-autumnal malaria which was very resistant to quinine; ultimately she received 90 gr. a day by injection and mouth over a period of seven weeks. This baby, as well as we could determine, seemed to be more or less deaf for about six months; but ultimately the condition cleared up and he is now, at seventeen months, perfectly normal in hearing. This brings up the question of the possible regeneration of the nerve if the nerve was really damaged by the quinine.

There was a point not brought up which should be, since we are talking about quinine; that is, the suggestion that fetal death may be caused by quinine, as brought to our attention by Dr. King several years ago. I have had two definite and one probable cases of fetal death from this cause. When at the height of quinine intoxication (as indicated in the mother by deafness and tinnitus) the baby begins to move violently and suddenly becomes and remains still with disappearance of the fetal heart sounds, we have suggestive evidence that quinine may cause death of the unborn infant. Since quinine does not have any material effect as an oxytocic in strengthening the contractions, and may be dangerous to the fetus, its use in obstetrics should be discouraged. I should like to see experiments carried out on another series of animals with the view of establishing quinine as a possible cause of fetal death.

Fränkel, W. K.: Urethral Inflammations and Strictures in Women, Wien. klin. Wchnschr. **48:** 1463, 1936.

In spite of its easy accessibility lesions of the female urethra are often overlooked. The bladder is frequently incorrectly treated when treatment should be directed towards the urethra. Seemingly functional bladder disturbances may be caused by inflammatory urethral changes. Skene's glands infections and gonorrhea in the female are essentially diseases of the urethra. Only in rare cases does gonorrheal urethritis give rise to a cystitis. Urethritis may occur in acute infectious diseases such as diphtheria and scarlatina and may also follow focal infections. Inflammatory changes in the urethra do not merely produce pain in the urethra but may give rise to pain higher in the urinary tract viz.; bladder, ureters, and kidneys.

If simple methods of diagnosis fail, the urethrocystoscope must be used. The therapy of urethritis is fairly simple; alkalization of the urine with sodium bicarbonate is worth while. This treatment removes the effect of acid irritating urine; while this may be given by mouth, local applications of iodine-silver-gelatin may be used in the urethra. Bladder irrigations may be given with various mild irrigants. Prophylactically reinfection should be avoided and dietotherapy should be carried out. Urethral strictures must be looked for and treated; the urethra may be dilated with a soft rubber catheter or small Hegar dilator; diathermy may also be employed. These treatments are carried out under local anesthesia. If syphilis is a factor, this should of course be treated by established methods.

W. B. SERBIN.

STERILIZATION OF OBSTETRIC PATIENTS IN VANDERBILT UNIVERSITY HOSPITAL 1925-1937*

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A STUDY of 100 obstetric cases sterilized in Vanderbilt University Hospital from October, 1925 to March, 1937 is the basis for this paper. All the patients were sterilized by operations on the Fallopian tubes, the abdominal approach being used in some instances and the vaginal approach, in others. The indications for sterilization are divided into eleven groups, and the cases will be discussed under their particular classifications.

Of the 100 cases reviewed in this report, 71 patients were sterilized by the abdominal route and 29 by the vaginal route. It has been concluded within the last five years that the vaginal method should be used whenever possible. In this period, that is, within the last five years, 33.4 per cent of the sterilizations have been vaginal. This is in sharp contrast to the sterilizations for the first half of the period of study, when only 10.5 per cent were done by the vaginal method.

There is considerable overlap in the indications for sterilization. For example, one tuberculous patient was feeble-minded and epileptic. Another tuberculous patient had a funnel pelvis. Such cases were listed under the classification of tuberculosis as well as in other groups.

It must be remembered that one indication alone may not be sufficient cause for sterilization but that, considered with other indications, it does warrant sterilization. Likewise, in many instances, a condition might indicate vaginal sterilization, where a combination of conditions would make abdominal sterilization advisable.

Table I. Sterilization—Indications and Methods

Indication	Number of Sterilizations		
	Abdominal Method	Vaginal Method	Total
Pulmonary tuberculosis	23	6	29
Tuberculosis of spine	2	0	2
Toxemia of pregnancy	19	9	28
Cardiac lesions	6	10	16
Diabetes	2	1	3
Pelvic deformities	8	0	8
Abnormalities of the soft parts	5	0	5
Previous cesarean sections	11	0	11
Social and economic conditions	1	2	3
Request of patient	3	2	5
Miscellaneous	4	0	4

*Read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

Pulmonary Tuberculosis.—Among the patients with pulmonary tuberculosis who were sterilized, 79 per cent were done by the abdominal route and 21 per cent by the vaginal route. The majority of the abdominal cases were done in the early part of the period under consideration. There is no intention to enter into a detailed discussion of the methods of delivery, but experience has shown that it is safer for some of these patients to be delivered vaginally, assisted by sedation, low forceps and episiotomy, and subsequently to be sterilized by the vaginal route. It is felt that active pulmonary tuberculosis is an indication for sterilization in almost every instance, especially in the indolent and ignorant class of patients[12] who cannot be relied upon to carry out contraceptive measures. Cesarean section is indicated when the condition is in a far advanced stage, as in patients with artificial pneumothorax, where long labor is expected (as in a primipara).

Although the average medical consultant is prone to advise cesarean section in tuberculous patients, our experience has shown that abdominal section is much more hazardous for these patients than is a delivery through the natural passages with elimination of the second stage of labor.

Tuberculosis of Spine.—The two cases listed as tuberculosis of the spine were sterilized primarily for reasons listed under other classifications and therefore will not be discussed here.

Toxemias of Pregnancy.—Under the heading of toxemias of pregnancy, three general types are included: (1) pre-eclamptic, (2) nephritic, and (3) eclamptic. The information concerning previous pregnancies given in the histories was not sufficient in every instance to differentiate the pre-eclamptic from the nephritic. Of the 28 patients with toxemia, 12 had cesarean section, 3 had associated abdominal operations, and 4 had hysterotomy. The latter 4 had nephritic toxemia, did not improve under treatment, and therefore required interruption of pregnancy (it has been the routine in such cases to do an hysterotomy with sterilization at the same time; this procedure has seemed safer in the majority of cases than the induction of abortion, followed at a later date by sterilization). Nine of the 12 patients who had cesarean sections had indications which, combined with the toxemia, made abdominal delivery necessary; the other 3 patients should have been delivered through the normal passages and subsequently sterilized vaginally. Nine patients with toxemia had vaginal sterilization, the preferable method.

It seems to be generally agreed that patients with nephritic toxemia should be sterilized. The authors are of the opinion that patients with eclamptic toxemia should also be sterilized, since the incidence of nephritis following the toxemia in these patients is exceedingly high.[9] These sterilizations should be carried out by the abdominal route only where other attendant conditions make this method imperative.

Cardiac Lesions.—Cardiac patients who stand up well under a physical strain should be delivered vaginally. The question of whether or not cardiac patients have more rapid and easier labors than do normal patients seems to be a debatable one, with apparently good evidence on both sides. Corwin and co-workers state that "cardiac cases have as a rule easy labors."[3] Daly remarks that "labor is usually shorter and less strenuous in cardiacs and . . . is a factor that can be controlled by good obstetrics."[4] MacLennan considers it "of considerable importance to note that labor in a patient suffering from cardiac disease is frequently short and precipitate."[5] On the other hand, Nelson and Eades, basing their observations on 530 cases of organic heart disease, do not find that cardiac patients have shorter or easier labor than normal women.[10]

The authors are inclined to agree with those investigators who maintain that labor is less strenuous and shorter in cardiac cases. On this basis, 62 per cent of the cardiac patients in this study were delivered through the natural passages and subsequently sterilized vaginally. In 38 per cent the following complications made other methods advisable: one patient had mitral stenosis and insufficiency with threatened heart failure; another had rheumatic heart disease, complete heart block and toxemia of pregnancy. It was felt that neither of these two patients could undergo labor and that cesarean section was therefore indicated. A third patient was delivered vaginally, with the intention of sterilizing vaginally, but an old pelvic inflammatory disease made this impossible. The fourth patient should have been delivered and

sterilized by the vaginal route. Hysterotomy and abdominal sterilization were done on two patients with hypertensive cardiovascular disease who could not go to term.

Diabetes.—In diabetic patients, sterilization should be strongly considered when the disease has been particularly difficult to control, when pregnancy aggravates the condition, or when both patient and husband are diabetic. Many authorities go so far as to say that in *all* diabetic patients further childbearing is contraindicated.[6, 7] The babies of diabetic mothers usually become very large and die ante partum. For this reason cesarean section is frequently necessary to save the baby, as was true in two of our cases. The third patient had a mild diabetes, had a small baby, and therefore was delivered and sterilized vaginally.

Pelvic Deformities.—Eight patients in our series had pelvic deformities. Of these, two had narrow, flat pelves, and both had had previous sections. One patient had a funnel pelvis and pulmonary tuberculosis. Five patients had generally contracted pelves (three had had previous sections, one was an imbecile and one was a rachitic dwarf with toxemia of pregnancy). In all these cases pelvic deformities, plus other conditions, made cesarean section and abdominal sterilization imperative.

Abnormalities of the Soft Parts.—Cesarean section was the only possible method of delivery of the 5 patients classified under the heading abnormalities of the soft parts. Other complications made sterilization necessary. Briefly, these cases were: one patient with double vagina, very large baby, previous section and requested sterilization. One patient had postoperative cervical scarring and pre-eclamptic toxemia. A third patient was obese, had stricture of the vagina, umbilical hernia repair and requested sterilization. A fourth patient had marked varicosities of the vulva, a brain tumor and tuberculosis. The fifth patient had marked varicosities of the vulva, had several children, and requested sterilization.

Previous Cesarean Sections.—"Once a cesarean, always a cesarean" has many advocates. However, "when the first was done for some reason such as placenta previa which does not exist in a subsequent pregnancy, and when her convalescence from the cesarean section was normal, the matter of permitting this patient to enter labor and deliver naturally must be entertained."[13] The patient should be followed carefully throughout subsequent labors and if, at any time, there seems to be an impending rupture of the uterus, section should be done. In 10 of our cases of abdominal sterilization which had had previous section, the condition for which the section was done still existed: among these conditions were deformities of the soft parts and pelvis, toxemias, and threatened rupture of the uterus. The other patient requested sterilization; she probably should have been delivered naturally and sterilized vaginally. It seems to be the general opinion that the third and fourth cesarean sections should be accompanied by sterilization.

Psychiatric Conditions.—The defense of eugenical sterilization seems based on the arguments that conditions such as insanity, feeblemindedness and epilepsy are increasing; that these conditions are mainly hereditary; and that such defective people propagate at a greater rate than does the normal population.[2] Feebleminded and epileptic patients comprised by far the majority of the patients sterilized by us for psychiatric conditions. The remainder had anxiety neuroses, in which the fear of pregnancy was the outstanding symptom. Seven patients were sterilized vaginally. Nine patients were sterilized abdominally; of these, 5 patients had associated eclampsia, abnormalities of the pelvis or tuberculosis. The remaining 4 patients were imbeciles; it was felt that they could not be relied upon to carry out contraceptive measures, and they, therefore, had cesarean section and abdominal sterilization. All the sterilizations in this group were done in consultation with a psychiatrist.

Social and Economic Conditions.—Three patients were sterilized because of social and economic conditions. These conditions included deaf mutism of the patient, mental deficiency of the patient's husband, and blindness of both patient and husband.

Request of the Patient.—There were 5 patients who were sterilized at their own request. One had had two previous sections which, as has been stated, is in itself generally considered an indication for section and sterilization. One patient had had 11 previous pregnancies, the last being terminated by cesarean section on account of placenta previa. One patient had had 5 previous pregnancies and was sterilized

abdominally in association with suspension of the uterus. The vaginal sterilizations were requested because of multiparity in one instance and a previous long, difficult labor in another.

Whether or not sterilization should be done simply because the patient requests it is a debatable question. In private patients the responsibility for the decision rests with the attending physician. The attitude of the Department of Obstetrics and Gynecology of Vanderbilt University Hospital is that in charity patients all phases, social, economic and psychologic, should be considered carefully before sterilization is carried out solely on the basis of the patient's request.

Miscellaneous.—There were 4 patients who did not fall in the above classifications. In studying the history, no reason could be found for sterilization in one case. Two patients had complete laceration of the perineum which had been repaired. One patient had a large ventral hernia. These four sterilizations were carried out by the abdominal route in association with an operation for suspension of the uterus.

OPERATIVE PROCEDURE

For sterilization, almost every known technique on the tubes has been used. Most of the operations were done by the Madlener-Walthard technique (crushing, ligation with nonabsorbable suture, and partial excision of the tube). Recently, however, the Pomeroy-Lull technique (ligation with absorbable suture and partial excision of the tube) has become the method of choice.

For the vaginal sterilizations reported in this study, the following procedure of operation was adopted.[1] The patient is placed in position and the usual preparation carried out. Up to the past year, the exaggerated lithotomy position was used; recently, however, the knee-chest position has been used, since in some instances it gives better access to the tubes. After a 1 to 1½ inch incision is made into the cul-de-sac of Douglas, the operation is done according to one of the techniques mentioned above. The peritoneum and vaginal mucosa are then closed in layers with plain catgut.

After the vaginal operation, the patient is propped up in bed at the end of twenty-four hours, placed in a chair at the end of forty-eight hours, and allowed to leave the hospital four to five days from the time of operation.

EFFECTS OF STERILIZATION

Discussion of the effects of sterilization upon the sex life of the woman is frequently found in the literature. However, clinical experience has shown that sterilization per se has no effect upon the sex reaction of most women. When a change in libido does occur, it is frequently increased rather than decreased. This is probably the result of the removal of the inhibitions due to the fear of pregnancy.

FOLLOW-UP OF CASES

Of the 100 patients sterilized by operations on the tubes, 89 have either been seen personally or have responded to a questionnaire sent them. Pregnancy has not occurred in any of these 89 patients. Five patients did not reply to the questionnaire and could not be found.

Six patients were found to have died in the twelve-year period. Some 5 or 6 cases included in the study are perhaps too recent to be considered as good material upon which to base any justifiable conclusion as to the efficacy of any method.

CONCLUSIONS

In conclusion, all operations for sterilization should be done only after a careful consideration of the condition of the patient with regard to congenital or acquired defects of the parturient passages, pathologic lesions of organs or systems of organs, and abnormal mental states. The social and economic factors should also be considered.

The vaginal approach for operations on the tubes is emphasized because of (1) the ease with which it may be carried out, (2) the minimal amount of discomfort to the patient, (3) its adaptability to any type of anesthesia, especially local combined with analgesia; (4) the greatly lessened risk to the patient of infection, since the greater peritoneal cavity is not opened, and (5) the short hospitalization necessary.

The Pomeroy-Lull method is advised, both in the abdominal and vaginal approach, because of its simplicity and effectiveness, as evidenced by results here and elsewhere.[5]

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DISCUSSION

DR. S. B. HINKLE, Little Rock, Ark.—Economic indications for sterilization are brought to us conscientiously and often by people, who have only the present economic situation in mind. It would be hard for me to accept as a reason for sterilization that the present economic condition in a particular family would not warrant future childbearing. It would, however, be acceptable if the economic conditions were permanent, as when due to irremediable disabilities, for instance, blindness, deafness, feeble-mindedness.

These essayists have, I am sure, given the opinion of this entire Association when they say that the request for sterilization may be made by an individual, but the reason must be evaluated by the surgeon.

DR. A. F. LASH, Chicago.—Since sterilization is an operation of choice we must be very certain that in performing it our mortality is practically nil. The combination of morphine and scopolamine with local anesthesia practically eliminates the anesthetic risk.

We do not think that toxemias of the pre-eclamptic type are necessarily an indication. Chronic nephritis, however, is definitely an indication to us. As Dr. Mc-

Clellan has brought out, while a small indication might not be reason enough to operate on an individual a combination of several will definitely indicate operation. We have now, as you well know, a proper management of diabetes and we can well permit a woman who desires children to have them.

DR. W. WORTHAM MAXWELL, SAN ANTONIO, TEXAS.—As a resident at Vanderbilt Hospital ten years ago, I operated upon one of these patients—a patient with active tuberculosis on whom we did a classical cesarean section with sterilization under spinal anesthesia. She lived about eight weeks, recovering entirely from the operation but died of a tuberculous pneumonia. The autopsy revealed several interesting features. The uterus had receded normally to the resting state; the omentum had attached itself along the site of the uterine incision and to each cornu where the medial portion of the tube had been resected. There were no other adhesions, thereby demonstrating how completely nature repairs our operative interference even in the presence of an extensive active tuberculosis.

DR. FREDERICK H. FALLS, CHICAGO.—In opening the peritoneal cavity through the vagina, we use local anesthesia, make an incision and proceed as if one were doing a Watkins-Wertheim interposition operation. This gives the advantage in many of these cases of finishing the operation by sewing the uterus anteriorly, thus giving support to the bladder and producing a cure of the associated cystocele which is so often present.

Sometimes these vaginal sterilization operations are unsuccessful. We had a rather interesting experience in this regard. A woman became pregnant after a Watkins-Wertheim interposition operation had been done by a gynecologist. She entered our clinic, and we were at a loss to know how to handle the situation. She had severe pain and was unable to void. I went in from below again, undid the Watkins-Wertheim interposition and pushed the uterus up into the abdominal cavity. At a later date I did a cesarean section and sterilization.

DR. LUCIUS E. BURCH (closing).—I desire to stress further the simplicity of vaginal sterilization. Recently we have placed the patient in the knee-chest position instead of the dorsal position for this procedure, which gives an easy access to the appendages. I should like also to emphasize the importance of not making traction on the tubes for the reason that it is likely to produce a tear of the mesosalpinx. The ovary should be found first, traction made upon it and then the tube will come down.

The operation as a rule is carried out under local anesthesia. We have not used the anterior method of sterilization unless hysterotomy was carried out at the same time. The anterior method of approach adds to the difficulty of the operation and the dissecting up of the bladder is time-consuming.

In regard to the efficiency of our technique of tying off the tube, our statistics are not worth much because they are too few in number. We are now using the Lull-Pomeroy technique. In other institutions where there has been a large series of cases, this technique has been successful, although there has been one recent report of a case of extrauterine pregnancy that followed the Lull-Pomeroy technique.

A STUDY OF 288 PRIMIPARAS OVER THE AGE OF 35 COMPARED WITH 300 PRIMIPARAS UNDER THE AGE OF 25*

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(From the Evanston Hospital)

THE obstetrician is called upon from time to time to assume the responsibility of a case of pregnancy when the woman is having her first baby late in her reproductive life. Does he assume an increased risk and, if so, what are the principal factors?

This study was made in a private hospital with a closed staff where the majority of the cases are handled by a small group of trained men who do nothing but obstetrics and gynecology. The period of time during which these 288 primiparas, over 35 years of age, were delivered was about sixteen years. The 300 primiparas under the age of 25, used for comparison, were consecutive cases of the same character, but their delivery dates do not correspond to the same years. They were delivered by the same men, however, and during a shorter period of time.

TABLE I. DURATION OF LABOR, INCIDENCE OF LABOR, AND CESAREAN SECTION COMPARED

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Number of cases	300	237	51
Duration of labor:			
Average	12 hr.	14 hr.	18 hr.
Shortest	1 hr.	1 hr.	1 hr.
Longest	72 hr.	52 hr.	73 hr.
Toxemia	2.3%	10.9%	13.7%
Cesarean sections	2.0%	17.3%	29.4%

Table I shows that the average length of labor is increased, but the duration of labor is of little importance. It is quite important, however, to note that toxemia increases with age. Admitting that the cause of eclampsia is yet unknown, we must assume that the excretory function decreases in efficiency as one's body grows older. The incidence of cesarean section does not increase because of necessity but probably because of fear both on the part of the doctor as well as the laity. It increases also because more of the risk is put on the mother and less on the baby, in order to assure a living child and what, in many cases, will be that family's only offspring. It increases also because malpresentations and toxemia increase. It is fairly safe to assume that any group of doctors skilled in the same surgical specialty would also show the same increased incidence of sections. Table IV gives the reasons for cesarean section recorded on the charts.

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

TABLE II. INCIDENCE OF PREMATURITY, FETAL AND MATERNAL MORTALITY, HEMORRHAGE, AND MORBIDITY

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Premature delivery (prior to 36th week)	4.4%	13.5%	19.6%
Gross fetal mortality	4.0%	7.9%	7.8%
Gross maternal mortality	0.0	0.4%	3.9%
Post-partum hemorrhage	2.6%	3.4%	5.8%
Febrile morbidity excluding cesarean sections	5.3%	5.1%	5.8%

Table II shows that the incidence of prematurity increases with age and that factor alone might account for the second row of figures showing an increase in fetal mortality; because when the gross fetal mortality is broken down into unavoidable and obstetric, the increase is found in the unavoidable group as shown in Table V.

TABLE III. PRESENTATION AND TYPE OF DELIVERY

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Spontaneous and low forceps deliveries	89.0%	69.0%	52.9%
Other deliveries	11.0%	31.0%	47.1%
Placenta previa	0.3%	0.4%	1.9%
Presentations:			
Anterior cephalic	80.6%	62.0%	49.2%
Posterior cephalic	10.4%	25.0%	27.4%
Breech and others	7.0%	5.0%	11.7%
Not stated	2.0%	8.0%	11.7%

Table III shows that malpresentations increase, which in turn leads to an increase in operative delivery. Why there should be more posterior cephalics, more breech presentations and other odd positions of the fetus among older primiparas, it is not possible to state.

TABLE IV. REASONS FOR CESAREAN

25 YR. OLD	35-39 YR. OLD	40 YR. AND OVER
1 Chronic nephritis	15 Toxemia	3 Toxemia
2 Toxemia	8 Fibroids	2 Test of labor
1 Breach with test of labor	3 Uncomplicated	2 Breech uncomplicated
1 Retinitis Pigmentosa	5 Complicated by other conditions	2 Transverse
1 Placenta previa	2 Breech uncomplicated	2 Fibroids
	11 Test of labor	1 Placenta previa
	1 Cardiac disease	3 Elective
	4 Elective	

TABLE V.

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Gross fetal mortality	4.0%	7.9%	7.8%
Unavoidable deaths	2.0%	5.4%	5.8%
Obstetric deaths	2.0%	2.5%	1.9%

Table VI shows the classifications of fetal deaths called "unavoidable."

TABLE VI. UNAVOIDABLE FETAL DEATHS

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Under 7 months	2	1	2
Dead before labor	3	2	
Monsters	2		1
Abruptio placentae at 8 months. F.H.T. lost in first stage.		1	

The 13 cases of fetal death, classed as obstetric, were as follows:

CASE 1.—Full-term infant weighing 7 pounds 5 ounces delivered after a labor of eleven hours. N_2O and ethylene used. Occiput posterior with manual rotation and forceps. Fetal heart tones very slow and could not be resuscitated. Autopsy report asphyxia neonatorum.

CASE 2.—Full-term infant whose weight was not recorded. Delivered spontaneously after seven hours of labor. Pantopon gr. 1/6 and scopolamine gr. 1/300, given 1¾ hours before delivery. N_2O used. Required resuscitation and did very poorly, dying 13½ hours after birth. No autopsy.

CASE 3.—Full-term infant, weighing 8 pounds 3 ounces delivered by low forceps and episiotomy after five hours of labor. Pentobarbital gr. 7½, scopolamine gr. 1/150, given four hours before delivery. N_2O and ethylene. Infant cyanotic at birth and never did well. Died on third day in a cyanotic attack. Autopsy showed partial pulmonary atelectasis.

CASE 4.—A full-term infant weighing 8 pounds 14 ounces, presenting by breech. Labor lasted 12½ hours. Given morphine gr.¼ and atropine gr. 1/150, one and one-half hours before delivery. N_2O and drop ether used. Breech extraction was done and the head became arrested in the midpelvis. Forceps were applied and a dead baby delivered. Autopsy showed asphyxia neonatorum.

CASE 5.—A 4 pound-14 ounce baby, born four weeks, prematurely after a nine-hour labor. Delivered by low forceps and episiotomy. Infant died in twenty-four hours. Autopsy showed prematurity, bilateral laceration of tentorium, intracranial hemorrhage and pulmonary atelectasis.

CASE 6.—A full-term infant delivered by low forceps after a rather difficult labor of thirty-one hours. Infant did poorly and died fifteen hours later. Autopsy showed a hemorrhagic pneumonia.

CASE 7.—This infant was four weeks premature and weighed 6 pounds 5 ounces. Given pantopon gr. 1/3 and scopolamine gr. 1/150, three hours before delivery. N_2O and ether used. Spontaneous delivery after a fifteen-hour labor. Died 3½ hours later. No autopsy.

CASE 8.—A full-term infant weighing 7 pounds 8 ounces delivered after a labor of twelve hours. Given pantopon gr. 1/3 and scopolamine gr. 1/300, four hours before delivery. N_2O and ether used. With head above the spines, B.O.W. ruptured artificially and the cord prolapsed. Forceps applied and a stillborn infant delivered.

CASE 9.—This infant was four weeks premature. The duration of labor was not stated. Infant weighed 4 pounds 1 ounce, delivered spontaneously and lived but seven hours. Autopsy findings were prematurity, cerebral hemorrhage and pulmonary atelectasis.

CASE 10.—A full-term infant according to due date. Delivered after an eighteen-hour labor by low forceps and episiotomy after about three hours in second stage. N_2O and ethylene used. Fetal heart tones were lost after forceps were applied. Infant was stillborn and not weighed. No autopsy.

CASE 11.—This infant was thought to be at term and was delivered by elective low cervical cesarean section because of a rather small pelvis. Infant weighed only 4 pounds 12½ ounces and lived only 5½ hours. Autopsy showed fluid in respiratory tract and cause of death given as asphyxia neonatorum.

CASE 12.—Full-term infant weighing 8 pounds 7 ounces delivered by breech extraction after a seven-hour labor. Both arms extended above head during extraction. Stillborn infant. Autopsy showed tentorial laceration on right side, subdural hemorrhage and asphyxia neonatorum.

CASE 13.—A full-term infant weighing 6 pounds 11 ounces. Mother had a premature rupture of B.O.W. with loss of most of amniotic fluid. A dry labor of twenty-five hours or more, terminated by manual dilatation of cervix and a high forceps application. Mother's heart decompensated during labor, but recovered. During six hours before delivery patient received 7/12 of a grain of morphine. N_2O and ether used. Infant stillborn. Autopsy of infant showed cerebellar damage. Hemorrhages in leptomeninges and beneath scalp.

There were no maternal deaths among the 300 primiparas under 25, and three deaths of mothers 35 and over. All three of the mothers who died were delivered by cesarean section. Case histories are, briefly, as follows:

Mrs. C. H., aged 40, para i. Admitted Jan. 5, 1922. Pre-eclamptic toxemia. Albumin ++. Blood pressure 158/98. Edema. Cesarean section Jan. 6, 1922, and two fibroids removed at time of section. Jan. 7, 1922, marked abdominal distention. Restlessness and by 8:00 P.M. pulse very rapid and patient in shock. Jan. 8, 1922, at 2:00 A.M. patient died. No post mortem. Abdominal incision opened and no abdominal pathology noted. Cause of death given as acute cardiac dilatation.

Mrs. J. B., aged 37, para i. Admitted July 8, 1931, at term. Mitral (rheumatic) disease and pre-eclamptic toxemia. Albumin ++. Blood pressure 158/106. Anesthetic one hour. Ethylene. No complications during cesarean section. Postoperative course marked by emesis and distention on second day. Given gastric lavage repeatedly and intravenous and subcutaneous fluids. On third day postoperative temperature and pulse began to rise and patient died on fifth day. Temperature reached 107° F. terminal. Blood transfusion was being given at time of death. Autopsy showed multiple pulmonary embolism, hemorrhagic infarcts of the right lung (involving 75 per cent of right upper lobe), thrombotic endocarditis of the mitral valve, mitral stenosis.

Mrs. M. H., aged 40, para i. Admitted Apr. 8, 1923. Transverse position. Cesarean section done April 10, 1923. Very smooth postoperative course. Up in chair on April 21. Sudden pain in chest, cyanosis, dyspnea, and death in fifteen minutes. Post mortem refused by husband. Signed out as pulmonary embolism.

Among the 288 patients over the age of 35, there were 19 in whom the presence of fibroids was a complicating factor; whereas, among the 300 young primiparas there were no cases recorded. Among these 19 cases there were 11 cesarean sections. Five of these women had toxemia also, an added reason for section. Four of the other 8 patients were delivered by forceps and 4 were spontaneous. Six of these cases could not be traced, but the other 13 were disposed of as follows:

Myomectomy at time of cesarean section	3 cases
Porro cesarean section	1 case
Subsequent hysterectomy	3 cases
Subsequent myomectomy	1 case
Tumors still present when last seen	3 cases
Spontaneous involution	2 cases

A word of caution should be spoken about myomectomy at the time of cesarean section. Subsequent myomectomy is safer, due to the profuse hemorrhage that generally occurs when one attempts to remove fibroids at the time of cesarean section. The fibroid generally undergoes marked involution at the same time as the uterus.

Only 25 of the 51 patients, delivering for the first time at the age of 40 or over, could be traced. Twenty of these stated that both mother and offspring were well. One mother said that her baby, now 13 years of age, had been an invalid since birth by cesarean section; the nature of the invalidism was not given. One mother refused to give any particulars about her welfare or that of her baby. Three patients had developed cancer and two of these had already died. The third patient was recently operated upon for cancer of the rectum.

CONCLUSION

1. When one assumes the responsibility for an obstetric patient who has her first baby in the later years of her reproductive life, one assumes more responsibility than if the patient were at the age of 25 or under.

2. The incidence of toxemia, prematurity, post-partum hemorrhage, malpresentation and myomas in primiparas, increases with the age of the individual.

636 CHURCH STREET

DISCUSSION

DR. RUDOLPH W. HOLMES, CHICAGO.—For many years I have taught students that they will have the same ease or difficulty, whether an obstetrical patient be 15 or 45 years of age. In other words, the bony structure, from an obstetric viewpoint, is fixed by the time the young woman enters the childbearing period except for the remote possibility of the development of osseous pelvic tumors or of true osteomalacia. Likewise, the soft parts retain their texture during the entire reproductive period except for rare instances of lesions appearing in later life. My conviction has been, therefore, that mere age has a very trivial influence on the type of labor. This belief is contrary to common teaching, but there have been numerous treatises, covering large series of case reports to substantiate my position. It is true, of course, that women who reproduce after 35 will have a somewhat higher incidence of cardiac, nephritic, and hepatic diseases, which complicate the conduct of their labors, but will not affect the type of labor.

It is, of course, true that an elderly primipara may require special management to safeguard her possible last chance of reproduction, a type of management which would be unjustifiable, yes unscientific in a much younger woman.

PELVIC MEASUREMENTS OF 4,144 IOWA WOMEN*

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THERE are so few reports from the United States of large series of pelvic measurements it is felt another is warranted. This seems especially true with regard to the present series which was obtained from women who represent predominantly a rural population. According to the 1930 official census 60.4 per cent of the inhabitants of Iowa live in communities of less than 2,500 population, and 39.6 per cent actually live on farms.

Therefore the purposes of this report are: (1) to present the average pelvic measurements of Iowa women, (2) to discuss the incidence of contracted pelvis in Iowa, and (3) to note the effect of pelvic contractions managed conservatively on labor, mother and child.

SUBJECTS

Between July 1, 1926, and Aug. 1, 1936, 6,426 women were delivered on the Obstetric Service at the University Hospitals. The overwhelming majority of these women have had ample opportunity to be exposed to sunlight, but their dietary is probably inadequate in certain particulars and should be described. The carbohydrate intake of the average Iowan is excessive, due to the consumption of large quantities of potatoes and bread. The protein content of the diet, although apparently adequate, is derived largely from pork with a fat content above average. Although milk and dairy products are produced in quantity, the per capita consumption falls below that of such dairy states as Minnesota, Wisconsin, Illinois, and New York. During the spring and early summer small fruits and vegetables are eaten in average quantity, but during the late summer and winter the consumption becomes progressively more inadequate.

The women of the present series represent a group which is overwhelmingly white, largely American born, but of mixed ancestry. The percentage of negroes in the population and in the present series is so small that it has been disregarded in the statistical analyses.

Among the 6,426 women, the pelvic measurements of 4,144 were considered to be sufficiently accurate to be available for the purposes of the study.

Of the total group of 6,426 women, 234 or 3.65 per cent had some type of contracted pelvis. Although seven of this group died undelivered or were delivered elsewhere, the measurements are included.

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

METHODS

Accurate mensuration of the pelvis in the living subject requires considerable practice. Therefore, for the purposes of this study, measurements made by a member of the department staff lower in rank than resident were not considered sufficiently accurate and were excluded. The obstetric resident in each instance had served at least three hospital years (two in obstetrics) and had had reasonable opportunity to develop the technic of pelvic mensuration.

Seven pelvic measurements are commonly made: the interspinous, intercristal, external conjugate or Baudelocque's diameter, bisischial or transverse diameter of the outlet, anterior sagittal, posterior sagittal, and anteroposterior. The intertrochanteric measurement is not done routinely. Determinations of 4,144 of each of the seven common pelvic measurements were available for statistical analysis.

In addition, the diagonal conjugate is measured routinely when the patient is admitted prior to the tenth lunar month of pregnancy, or if there is indication of contracted inlet such as non-engagement of head in a primigravida, or obvious disproportion. However, the majority of this group were admitted within the last month of pregnancy so that, in the absence of indication of contracted inlet, measurement of the diagonal conjugate was not done. Therefore, only 972 attempts were made to measure the diagonal conjugate, and of these the sacral promontory was beyond reach of the examining finger in 865 patients.

In addition, individual study of each contracted pelvis was made in order to ascertain the incidence of the various types, the effect on the clinical course of labor, and on the mother and child.

RESULTS

1. *Average Pelvic Measurements of Iowa Women.*—The average pelvic measurements, the range, and probable errors are recorded in Table I, and with the exception of the bisischial agree closely with common teaching. However, a textbook of obstetrics[1] in general use states, "The transverse (bisischial) diameter measures 11 cm." In the present series of 4,144 women the chances statistically are twenty-one to one that the true mean of the series lies between 7.77 and 10.84. Therefore, there seems to be very little justification for assuming 11 cm. to represent the true measurement of the transverse (bisischial) diameter of the pelvic outlet of Iowa women.

With the bisischial measurements, tests for normality of the series showed that B_1 equals 0.101 and B_2, 3.067. The value of B_2 falls well within the 5 per cent limits of the Pearson[2] criterion for normality, while the value of B_1 falls outside the 1 per cent limit. Therefore, the chances are reasonable that the observations are normally distributed.

TABLE I. AVERAGE PELVIC MEASUREMENTS OF 4,144 IOWA WOMEN (CENTIMETERS)

Note that with the exception of the bisischial measurement, these results agree closely with common teaching.

	AVERAGE	PROBABLE ERROR	RANGE
Interspinous	25.5	1.09	21.0-31.5
Intercristal	28.0	1.14	19.5-34.0
External conjugate	19.6	0.85	15.0-25.0
Bisischial	9.3	0.51	6.0-12.0
Anterior sagittal	6.2	0.43	4.0- 9.5
Posterior sagittal	7.8	0.38	5.5-10.0
Anteroposterior	11.4	0.43	8.0-13.5

Although it has generally been conceded that agreement within a half centimeter between any two staff members represents as high a degree of accuracy as may rea-

sonably be expected, it is common practice to attempt measurement of the various pelvic diameters in quarter, or even smaller fractions of a centimeter. Such refinements in technic do not represent greater accuracy, as they are generally subjective estimates rather than objective measurements. This point is demonstrated admirably when measurements are plotted in a frequency bar diagram, and is illustrated in Charts 1 and 2 in the case of the bisischial diameter. Chart 1 shows the class fre-

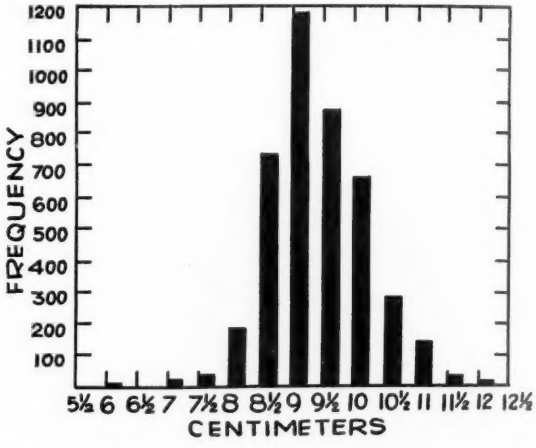

Chart 1.—Showing a frequency diagram of 4,144 bisischial measurements plotted in quarter-centimeter divisions. Note that there is a distinct negative bias.

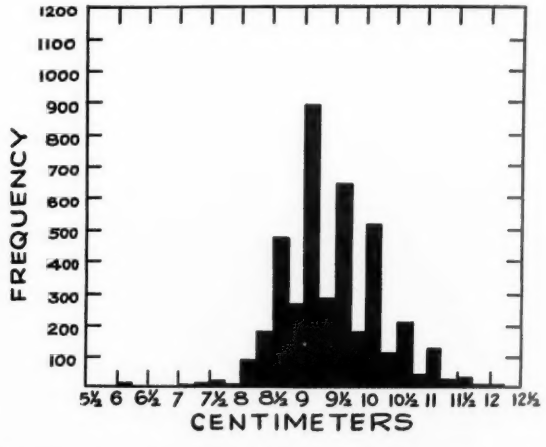

Chart 2.—The quarter-centimeter divisions of Chart 1 have been eliminated by adding half of the frequency of each to the next higher, and half to the next lower class. Note that the frequency distribution is more nearly normal, suggesting that recording of pelvic measurements in less than half-centimeter divisions represents subjective estimation.

quency when plotted as measured. It will be seen that there is a distinct negative bias in the quarter and three-quarter divisions. Chart 2 shows the same data regrouped into half-centimeter divisions. The frequency in each quarter and three-quarter division was divided by two, and half of each of these frequencies allotted to the next higher and half to the next lower division. It is apparent that by so doing, the frequency distribution is more nearly normal. Consequently, it is sug-

gested that even an observer with years of experience in pelvic mensuration is beyond the limits of reasonable accuracy when recording measurements in fractions smaller than a half centimeter.

Because of the small number (972) of attempts to measure the diagonal conjugate and because in 865 of these attempts the sacral promontory was not reached, the figures for the diagonal conjugate were not submitted to statistical analysis, but are recorded in Table II.

TABLE II. DIAGONAL CONJUGATE*

Note that although 972 attempts to measure the diagonal conjugate were made, only 71 measured 11½ cm. or less.

DIAGONAL CONJUGATE MEASURED LENGTH CM.	NUMBER OF PATIENTS	DIAGONAL CONJUGATE MEASURED LENGTH CM.	NUMBER OF PATIENTS
6½	1	11	17
8	1	11¼	8
8½	1	11½	13
9	1	11¾	3
9¾	2	12	14
10	6	12¼	5
10¼	4	12½	13
10½	13	12¾	1
10¾	4	Total	107

*In 865 additional patients, the diagonal conjugate could not be reached.

2. *Incidence of Contracted Pelvis.*—Any patient whose routine measurements suggested contracted pelvis, or who experienced unusual difficulty during labor, was rechecked. In all, 234 patients (3.65 per cent) with contracted pelves were noted among the total group of 6, 426 women. This figure, the total number of women delivered during the given time period, was used to calculate the incidence of pelvic contraction rather than 4,144, the figure on which the statistical calculations of the normal pelvic measurements are based. The reasons for using the figure 6,426 in calculating the incidence of contracted pelvis are: (1) it represents the *total* number of women delivered during the given period of time, (2) it is felt that the rechecking of pelvic measurements following difficult labor gives reasonable assurance that 234 represents the *total* number of women with contracted pelves observed during the same period. The criteria adopted for inlet contraction were those advanced by Litzmann,[3] viz.; the true conjugate measures 9.5 cm. or less in flat, and 10.0 cm. or less in generally contracted pelves. Williams[4] advanced the criterion adopted for outlet contraction, viz.; a bisischial (transverse) diameter of 8.0 cm. or less.

Table III shows the total incidence of pelvic contraction as well as the relative incidence of each type, contrasted with the figures for white women given by Williams.[1] Although the total number of women in each series is nearly identical, pelvic contraction was noted nearly four times as frequently in the Hopkins as in the Iowa clinic. Reynolds[5] reporting on 2,227 Boston women gives an incidence of contracted pelves among patients requiring obstetric operations of 1.7 per cent, but had he included all of his patients, the incidence would have been 6.8 per cent. Flint[6] reported an incidence of 8.46 per cent among 10,233 women in New York City. In both Reynold's and Flint's papers funnel pelves are not included, as their reports antedate by nineteen and twelve years, respectively, Williams'[4] contribution on contractions of the pelvic outlet. Revision to include the usually accepted figures for incidence of funnel pelvis would raise Reynold's estimate to 11 or 12 and Flint's to 14 or 15 per cent.

The explanation for the low incidence of pelvic contraction among the women of the present series is obscure. Adequate formation of pelves of Iowa women is presumably not due to dietary measures, as the average diet tends to be deficient in minerals and vitamins. Iowa children, however, apparently have ample opportunity, because the population is essentially rural, to be in the sunlight. Whether or not

TABLE III. INCIDENCE OF CONTRACTED PELVIS

Note that pelvic contraction occurs nearly four times as frequently in the Hopkins as in the Iowa clinic. Although accurate measurements were available for only 4,144 women, the total number (6,426) of women delivered during the given period of time was used to calculate incidences of contracted pelves as it was felt that 234 represents *all* of the contracted pelves observed during this time.

	JOHNS HOPKINS* 6,407 WHITE WOMEN			IOWA 6,426 WOMEN		
	NUMBER OF PATIENTS	IN-CIDENCE	PER CENT OF CON-TRACTED PELVIS	NUMBER OF PATIENTS	IN-CIDENCE	PER CENT OF CON-TRACTED PELVIS
Generally contracted, including generally contracted funnel	345	538	39.98	41	0.64	17.5
Funnel, typical	289	5.03	33.49	156	2.43	66.7
Simple flat	156	2.43	18.07	25	0.39	10.7
Generally contracted rachitic	33	0.52	3.82	1	0.02	0.4
All others	40	0.63	4.63	11	0.17	4.7
Totals	863	13.99	99.99	234	3.65	100.0

*From Stander, H. J., *Williams Obstetrics.*

such exposure is significant is debatable. Another possible explanation of the difference in incidence involves the element of time, for, with rickets less common than formerly, statistics collected forty or more years ago may show a greater incidence of pelvic contractions on a rachitic basis.

Although typical funnel pelvis is generally thought to be a developmental phenomenon and to have similar incidences among all reported races, 5 to 6 per cent, the incidence among the present series is 2.44 per cent, less than half that reported by other observers. Even when all types of funnel pelves are included the incidence is only 2.55 per cent. It is conceivable that the method of measuring the bisischial diameter differs slightly from that used elsewhere, and that this may account for the low incidence of funnel pelves. With this in mind, the number (186) of pelves with bisischial diameters of 8.25 cm. was added to those (156) previously classified as funnel. The resulting total (342) gives an incidence of 5.33 per cent, a figure which agrees closely with that generally given. On the other hand, by adoption of the statistical method previously used, namely dividing the frequency (186) of the 8.25 cm. division by two and allotting one-half (93) to the 8.0 cm. meter class and the remainder to the 8.5 cm. class, the total number of funnel pelves becomes 249, an incidence of 3.87 per cent, which is still below that generally given. No explanation is offered for the low incidence of this type of pelvic contraction among the group of Iowa women.

3. *Effect on the Clinical Course of Labor.*—Among the various types of contracted pelves, the incidence of operative interference, Table IV, ranges from 26.9 to 54.5 per cent. However, when low forceps operations and breech extractions are excluded, the range is from 20.0 to 36.4 per cent. Obviously, low forceps operations and breech extractions were not done because of the pelvic contraction, except in funnel pelves, where low forceps was employed to overcome outlet dystocia, and in one instance where version and extraction of the aftercoming head was necessary.

The average lengths of the first and second stages of labor were calculated for individuals representing each type of pelvic contraction, but no significant variations from normal were observed.

4. *Effect on the Mother.*—There were four maternal deaths among the group of contracted pelves, Table V, a gross maternal mortality rate of 1.7 per cent. One of these women was admitted at term in extremis from a four-year-old bilateral carcinoma of the breasts with extensive metastases. Her death, four days after low forceps operation done to shorten the second stage of labor, can hardly be associ-

ated with the funnel pelvis. Another woman died undelivered at term from a proved gas bacillus *(B. Welchii)* infection. The other two deaths were sequels of operations done because of the pelvic contractions. The corrected maternal mortality rate becomes, therefore, 0.85 per cent.

TABLE IV. OPERATIVE LABORS

Showing the number and percentage incidence of operations, presumably necessitated by the pelvic deformity.

	NUMBER OF PATIENTS	NUMBER							TOTAL OPERATIVE INCIDENCE		
		CESAREAN SECTION		FORCEPS			BREECH			PER CENT	
		CLASSIC	LOW	HIGH	MID	LOW	VERSION AND EXTRACTION	BREECH	NUMBER	UNCORRECTED	CORRECTED
Generally contracted, including generally contracted funnel	41	5	4	–	–	2	–	1	12	29.3	21.9*
Funnel, typical	156	12	–	–	3	20	1	6	42	26.9	23.1†
Simple flat	25	3	1	1	–	3	–	–	8	32.0	20.0*
Generally contracted rachitic	1	–	–	–	–	–	–	–	–	–	–
Miscellaneous	11	3	–	–	1	1	–	1	6	54.5	36.4*
Totals	234	23	5	1	4	26	1	8	68	29.1	23.1

*Low forceps and breech excluded.

†Breech excluded. The version, done because of the contraction, is included.

TABLE V. MATERNAL AND FETAL MORTALITY
(ACTUAL NUMBERS)

Showing the total number of maternal and fetal deaths in the series, and the number presumably attributable to the pelvic deformity.

	MATERNAL		FETAL	
	TOTAL	CORRECTED	TOTAL	CORRECTED
Generally contracted, including generally contracted funnel	0	0	3	0
Funnel, typical	2	0	14	5
Simple flat	1	1	0	0
Generally contracted rachitic	0	0	0	0
Miscellaneous	1	1	1	0
Total	4	2	18	5

5. *Effect on the Child.*—There were 18 stillborn and neonatal deaths, a gross fetal mortality rate of 7.8 per cent. However, of these, 4 were abortions (fetuses weighing less than 1,500 gm.), 4 were stillborn macerated fetuses obviously dead before the onset of labor, and 4 were premature infants (1,500-2,500 gm.). Three of the prematures who succumbed after birth were shown at post-mortem examination to have perished from prematurity alone, or from prematurity and atelectasis, and therefore, these deaths cannot be ascribed to the pelvic deformity. However, the fourth, weighing 2,248 gm., died the day after birth and permission for post-mortem examination was withheld. One infant with a prolapsed cord died before birth, as a result of compression of the cord with a Voorhees' bag inserted following replacement of the funis. Another stillbirth resulted from premature separation of the normally implanted placenta. These two deaths presumably may also be ex-

cluded. Four term babies died at birth or a few hours thereafter from intracranial hemorrhage. Therefore, these 4 and the 2,248 gm. premature on whom autopsy was not allowed, a total of 5, are the only fetal deaths directly attributable to the pelvic contraction. This represents a fetal mortality rate of 2.1 per cent possibly due to contracted pelvis.

The average weight of the newborn children showed no significant variation from normal.

SUMMARY AND CONCLUSIONS

1. The average pelvic measurements of a group of 4,144 living Iowa women were found to be: interspinous, 25.5 cm.; intercristal, 28.0 cm.; external conjugate (Baudelocque), 19.6 cm.; bisischial (transverse diameter of the outlet), 9.3 cm.; anterior sagittal, 6.2 cm.; posterior sagittal, 7.8 cm.; anteroposterior, 11.4 cm. With the exception of the bisischial, these measurements agree with common teaching.

2. The fallacy of attempting to measure pelves more closely than by half-centimeter divisions is pointed out, using the bisischial measurement as an illustration.

3. Among 6,426 women, delivered between July 1, 1926, and Aug. 1, 1936, there were 234 contracted pelves, an incidence of 3.65 per cent.

4. Typical funnel pelvis was the most common type, accounting for 156, or 66.7 per cent, of the 234 contracted pelves, or 2.43 per cent of the total series of patients. Generally contracted, including generally contracted funnel pelves, numbered 41, 17.5 per cent of the contracted group, or 0.64 per cent of the total series. Simple flat pelves numbered 25, 10.7 per cent of the contracted pelvis group, while the remaining 12 contracted pelves were of miscellaneous classification.

5. The uncorrected incidence of operative interference was 29.1 per cent. By excluding operations not directly indicated by the contracted pelvis, the corrected operative incidence was 23.1 per cent.

6. Two mothers perished from operations done because of the pelvic contraction, a mortality incidence of 0.85 per cent.

7. Five fetal deaths, a mortality rate of 2.1 per cent, were directly attributable to the pelvic contraction.

The author wishes to express his appreciation to Miss Maxine Ball for her assistance in collecting the data for this paper.

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DISCUSSION

DR. CALVIN R. HANNAH, DALLAS, TEX.—In my opinion the important point in this excellent paper is that the frequency of contracted pelves is probably about 3.5 or less than 4 per cent. Another excellent point he has brought out is the measurement of the outlet.

The physicians throughout Texas are probably no different from those of other states, but as we go about teaching through refresher courses it is astounding that the number of physicians who do not know how to make pelvic measurements is so great. We found in a class of 15 or 20 good physicians that less than three men knew how to make measurements. It is up to us as members of this Society to disseminate this information and to teach the men in the rural districts as well as those in the cities how to use a pelvimeter. They must understand that they cannot estimate the size of the pelvis by palpation but that they must do it by practical work and by measurements.

MANAGEMENT OF PLACENTA PREVIA*

An Analysis of 47,828 Cases

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NEARLY three centuries have passed since Paul Portal (1664) demonstrated for the first time that in placenta previa the afterbirth is embedded over the cervical os. Earlier observers, to the time of Hippocrates, recognized the seriousness of the condition but believed the resulting hemorrhages were due to the premature detachment of the placenta located, as they thought, in the fundus. The observations of Portal awakened a lively interest in placenta previa and we find Mauriceau, Pugh, Deventer, Smellie, Levret and a host of other obstetricians of the seventeenth, eighteenth, and nineteenth centuries advocating means of control of the hemorrhages and the speedy delivery of the baby and afterbirth.

While the records of earlier times reveal a marked improvement in results, as expressed in maternal and fetal mortalities, it may be said that it is in quite recent years that the greatest advances have been made. Great as has been this progress the maternal and fetal mortalities are yet far too high. Of this I became more convinced as I undertook an extensive statistical review of the literature. To the cases already recorded I have added 62, previously unreported, from the records of the Philadelphia Lying-in Hospital, covering a period from July 1, 1929, to June 30, 1935. It is hoped that this large series of cases, taken from the records of clinicians and institutions the world over, will throw some light on the treatment of placenta previa and the comparative results of the various methods now in common usage. All available statistics have been carefully studied and an impartial analysis has been made.

As will be shown later, the therapeutic trend has changed markedly in the past ten to fifteen years, with increasingly more satisfactory results for both mother and child. This change may be accounted for in several ways: (1) a better understanding of the pathology and

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symptomatology of the condition resulting in a greater number of early diagnoses, (2) a more universal appreciation of the dangers resulting from untimely interference, (3) improved operative technic, (4) marked advancements in the field of anesthesia, (5) recourse to blood transfusions, and (6) more adequate maternity facilities in the smaller communities. Fortunately, there is now little necessity for handling these cases in the private home under conditions which, even at best, are inadequate. This one factor alone has to a large extent reduced the incidence of infection, one of the two greatest complications.

I present the collected case reports under two headings: (1) those reported up to and including the year 1921, and (2) those reported from 1922 to the present time. These two groups of cases are sufficiently large, I believe, to give a fairly accurate picture of the types and results of the therapeutic measures in vogue during the respective periods.

It will be noted that no mention is made of the corrected fetal mortality, due to the circumstance that most of the reports failed to refer to this item. Instead, all fetal deaths of whatever period of gestation and under all conditions are grouped together.

There has been no unanimity in the classification of placenta previa. In my review, cases in which the placenta has completely covered the internal cervical os will be spoken of as *complete previas;* those in which the margin of the placenta has partially covered the internal os will be called *marginal previas;* and those in which the edge of the placenta borders on or touches the internal os will be classed as *lateral previas.*

The total number of cases reviewed is 47,828, or more than twice the number ever before collected. The frequency of the condition has been variously stated from 1 in 34 to 1 in 506 pregnancies. In a series of 21,706 cases I found the incidence to be 1 in 159.6 (0.626 per cent). In 9,513 cases 2,830 (29.75 per cent) were of the central type, 3,127 (32.87 per cent) were marginal, 3,525 (37.05 per cent) were laterals, and 31 (0.33 per cent) were of unknown classification.

Abnormal position of the fetus is common and may be considered as one of the suggestive diagnostic features. Cephalic presentations were found in 687 (71.19 per cent) of 965 cases, breech presentations in 130 (13.48 per cent), transverse lies were present in 146 (15.13 per cent), and in 2 (0.2 per cent) the position of the baby was not known.

A great predominance of cases was found in multiparas. In a total of 21,111 cases placenta previa was found to occur in 2,918 primiparas (13.82 per cent) and in 18,193 multiparas (86.18 per cent).

It has often been stated that placenta previa is a complication of the third trimester of pregnancy. This is the rule. However, it is well known that symptoms may arise at any time after the formation of the placenta. It was found to occur in 3,753 (84.98 per cent) of 4,416 cases after the thirty-first week of gestation and in 663 (15.02 per cent) prior to this period.

TABLE I. PLACENTA PREVIA

Cases before 1922:	
Number	15,062
Maternal mortality	1,166 (7.74%)
Gross fetal mortality	7,876 in 14,162 cases (55.61%)
Cases from 1922 to 1937:	
Number	32,766
Maternal mortality	2,288 (6.98%)
Gross fetal mortality	6,551 in 12,885 cases (50.84%)

Table I shows the total series of cases divided into the two group periods. It will be observed that in the past fifteen years both the maternal and fetal mortality rates have been definitely reduced. Upon further examination, and subdividing the cases into those delivered vaginally and those delivered by the abdominal route (see Table II), we can readily see that the major drop in the maternal death rate resulted from an increased adoption of cesarean section. Infant mortality decreased somewhat but not in proportion to the maternal rate. We also note that fewer mothers died after delivery from below. As will be pointed out later, this decrease resulted from the abandonment of certain traumatizing operative procedures, such as accouchement forcé and vaginal cesarean sections. These figures differ somewhat from those recently reported by Mackenzie, who found maternal and fetal mortalities of 6.6 per cent and 17 per cent, respectively, in cesarean sections, and 8 per cent and 53.7 per cent in those delivered by the vaginal route.

TABLE II. GROSS FETAL AND MATERNAL MORTALITY

Cases before 1922—4,627:	
Cesarean sections	281 (6.07%)
Maternal mortality	34 (12.09%)
Gross fetal mortality	75 (26.69%)
Vaginal deliveries	4,346 (93.93%)
Maternal mortality	343 (7.89%)
Gross fetal mortality	1,685 in 2,864 cases (58.83%)
Cases from 1922 to 1937—31,935:	
Cesarean sections	4,885 (15.29%)
Maternal mortality	293 (5.99%)
Gross fetal mortality	458 in 1,873 cases (24.45%)
Vaginal deliveries	27,042 (84.71%)
Maternal mortality	1,735 (6.41%)
Gross fetal mortality	4,869 in 8,477 cases (57.43%)

In Table III we find listed the various types of vaginal deliveries with their respective maternal and fetal mortalities. From this we learn that repeated, prolonged or complicated vaginal manipulations greatly enhance the risk to both mother and child. This is most noticeable in such methods as internal podalic version, accouchement forcé, ligation of the uterine vessels, craniotomy, and vaginal

TABLE III. VAGINAL DELIVERIES WITH MORTALITIES

METHOD	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
Spontaneous	3,068	70 (2.28%)	525 in 2,244 cases (23.39%)
Ruptured membrane	2,070	37 (1.78%)	436 in 1,958 cases (22.24%)
Pack	477	32 (6.71%)	239 in 475 cases (50.31%)
Bag	4,464	263 (5.89%)	1,542 in 3,113 cases (49.50%)
With spontaneous	28	1 (3.57%)	8 in 28 cases (28.57%)
With version	340	13 (3.82%)	77 in 214 cases (35.99%)
With forceps	35	2 (6.14%)	4 in 22 cases (13.63%)
With breech	14	2 (14.28%)	10 in 14 cases (71.42%)
Breech	644	35 (5.43%)	381 in 608 cases (62.66%)
Forceps	224	16 (6.55%)	83 in 197 cases (42.13%)
Braxton Hicks version	10,660	686 (6.43%)	5,523 in 8,213 cases (67.24%)
Version	3,210	359 (11.18%)	1,063 in 2,526 cases (42.08%)
Willett	263	12 (4.56%)	143 in 263 cases (54.37%)
Leg traction	500	36 (7.20%)	358 in 500 cases (71.60%)
Craniotomy	29	6 (20.69%)	29 in 29 cases (100.00%)
Accouch. forcé	291	71 (24.39%)	133 in 282 cases (47.16%)
Vaginal cesarean	1,324	95 (7.17%)	288 in 1,025 cases (28.09%)
Undelivered	22	22 (100.00%)	22 in 22 cases (100.00%)
Induction	15	0 (0.00%)	11 in 15 cases (73.33%)
Unknown			
Total	27,678	1,758 (6.35%)	10,877 in 21,748 cases (50.01%)

cesarean sections. In other words, the simpler the method used the greater is the chance for the survival of both mother and child. No definite causes of maternal mortality were stated, but it is presumed that the majority of the patients died from shock or infection.

TABLE IV. TYPES OF CESAREAN SECTIONS

Classical:		6,168
Maternal mortality	372 (6.03%)	
Gross fetal mortality	687 in 2,794 cases (24.58%)	
Low cervical:		375
Maternal mortality	7 (1.86%)	
Gross fetal mortality	11 in 67 cases (16.41%)	
Porro:		61
Maternal mortality	8 (13.11%)	
Gross fetal mortality	20 in 28 cases (71.42%)	

It is interesting to note that the incidence of cesarean section has more than doubled during the past fifteen years, and in spite of this great increase in number the maternal mortality has been more than halved; it falls well below the group delivered vaginally. The fetal mortality in abdominal cesarean sections was but slightly decreased but remained much lower than in the group delivered through other avenues. In Table IV we find a comparative list of the various types of abdominal cesarean sections. Although the series of low cervical sections is too small to permit of any definite conclusions it would seem, in the hands of skilled operators, to give both mother and child a better chance for life. The danger of a generalized peritoneal infection is greatly lessened by this procedure because there need be no manipulation of the intestines or omentum, and the general peritoneal cavity can be

TABLE V. TYPES OF PLACENTA PREVIA

METHOD	CENTRAL PREVIA			MARGINAL PREVIA		
	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
Spontaneous	17	0 (0.00%)	13 (76.47%)	175	4 (2.28%)	57 (32.57%)
Ruptured membranes	20	1 (5%)	10 (50%)	144	2 (1.39%)	70 (48.61%)
Pack	28	4 (14.28%)	14 (50%)	133	4 (3%)	80 (60.15%)
Bag	26	2 (7.69%)	12 (46.15%)	30	1 (3.33%)	16 (53.33%)
With spontaneous						
With version	7	1 (14.28%)	0 (0%)	6	0 (0%)	5 (83.33%)
With forceps				6	0 (0%)	1 (16.66%)
With breech						
Breech	8	1 (12.49%)	2 (25%)	7	0 (0%)	1 (14.28%)
Forceps	14	3 (21.42%)	12 (85.71%)	31	1 (3.22%)	18 (58.06%)
Braxton Hicks version	425	47 (11.05%)	362 (85.17%)	486	24 (4.95%)	345 (70.98%)
Version	92	14 (15.21%)	58 (70.72%)	76	2 (2.63%)	14 (18.42%)
Willett	15	1 (6.66%)	15 (100%)	143	7 (4.89%)	80 (55.94%)
Leg traction	132	10 (7.57%)	114 (86.36%)	65	0 (0%)	44 (67.69%)
Craniotomy	8	4 (50%)	8 (100%)	2	0 (0%)	2 (100%)
Accouch. forcé	5	1 (20%)	3 (60%)	2	0 (0%)	1 (50%)
Vaginal cesarean	2	1 (50%)	1 (50%)			
Classical cesarean	504	29 (5.75%)	116 (23.01%)	153	6 (3.92%)	21 (13.72%)
Low cervical	24	1 (4.16%)	1 (4.16%)	2	0 (0%)	0 (0%)
Porro	11	1 (9.09%)	3 (27.27%)			
Undelivered	2	2 (100%)	2 (100%)			
Induction						
Unknown	632	91 (14.39%)	97 (15.34%)	1739	66 (3.79%)	140 (8.05%)
Vaginal delivery	23	3 (13.04%)	?	27	1 (3.73%)	0 (0%)
Abdominal delivery	78	3 (3.84%)	12 (15.38%)	38	0 (0%)	4 (10.52%)
Total	2063	220 (10.66%)	806 in 2040 cases (39.51%)	3266	118 (3.62%)	899 (27.52%)

better protected against "spill" from an infected uterus. In event of frank infection the Porro operation seems to be the procedure of choice. No mention was found in the literature of the use of the Latzko operation in placenta previa.

In Table V we are able to contrast the results of all methods of management in the various types of previas. From them we may learn one important fact, namely, that the risk for mother and child increases in direct proportion to the degree of the previa. With but few exceptions, the various methods show a reduction in death rates in marginal as compared with complete previas and in lateral as against marginal cases.

Although there were no accompanying statistics there have recently appeared in the literature numerous references concerning the use of blood transfusions in the treatment of placenta previa. There is no doubt that frequent recourse to this life-saving procedure has prevented many casualties. In most maternity centers it is now a routine procedure to procure suitable donors for all suspected cases of placenta previa and to be prepared for immediate transfusion should the necessity arise. I am convinced that in the future this procedure will be more often adopted and will save many lives that are now lost by lack of foresight or inability to obtain suitable blood. It not only is the best method we possess for combating shock and acute anemias but is an excellent prophylactic measure against infection and prolonged convalescence. It should be more often resorted to.

With Treatment and Mortality

LATERAL			UNKNOWN		
CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
347	0 (0%)	83 (23.91%)			
285	7 (2.45%)	105 (36.84%)			
83	2 (2.41%)	36 (43.37%)			
56	1 (1.78%)	10 (17.85%)			
41	2 (4.87%)	2 (4.87%)			
5	1 (20%)	1 (20.0%)			
26	0 (0%)	7 (26.92%)			
55	4 (7.27%)	13 (23.63%)			
186	14 (7.52%)	104 (55.91%)			
78	6 (7.69%)	30 (38.33%)			
86	3 (3.48%)	42 (48.83%)			
81	2 (2.46%)	58 (71.60%)			
4	2 (50%)	4 (100.0%)			
5	2 (40%)	3 (60.0%)			
92	7 (7.60%)	11 (11.93%)	18	1 (5.55%)	0 (0%)
9	0 (0%)	0 (0%)			
2	0 (0%)	2 (100.0%)			
			1	1 (100.0%)	1 (100.0%)
15	0 (0%)	6 (40%)			
419	34 (8.11%)	182 (43.43%)	14	1 (7.14%)	3 (21.43%)
35	1 (2.85%)	0 (0%)	8	2 (25.0%)	0 (0%)
66	0 (0%)	8 (12.12%)	3	0 (0%)	1 (33.33%)
2096	88 (4.19%)	707 (33.73%)	44	5 (11.46%)	5 (11.46%)

SUMMARY

1. An analysis of the management and results of 47,828 cases of placenta previa collected from world-wide literature is presented.

2. The total series is divided into two groups: (1) those reported up to and including 1921, and (2) those reported from 1922 to the present time. The latter group shows a small but definite decrease in both maternal and fetal mortalities over the former. This decrease may be accounted for by (1) a better understanding of the pathology and symptomatology of the condition resulting in a greater number of early diagnoses, (2) a more universal appreciation of the dangers resulting from untimely interference, (3) improved operative technic, (4) marked advancements in the field of anesthesia, (5) recourse to blood transfusions, and (6) more adequate maternity facilities.

3. A subdivision of these two main groups into those patients delivered vaginally and those by the abdominal route is made showing the mortality rates of each. The incidence of cesarean section has increased from 6.07 per cent to 15.29 per cent during the past fifteen years while the maternal mortality rate has been more than halved and falls well below the group delivered from below. A slightly lessened maternal death rate was also noted in those patients delivered vaginally. This decrease is chiefly due to the avoidance of such methods as accouchement forcé, Braxton Hicks version, vaginal packs and vaginal cesarean sections. Tables revealing the results of both abdominal and vaginal methods indicate that repeated, prolonged or complicated manipulations greatly enhance the risks to both mother and child.

4. Further tables show the methods used in handling the various types of previas. With but few exceptions, the various procedures show an increase in mortality rates in direct proportion to the degree of the previa.

5. Low cervical cesarean section is the procedure of choice in complete placenta previa and in other types presenting a closed cervix. In marginal or lateral previas with a dilated cervix the method of choice is between artificial rupture of the membranes with forceps or spontaneous delivery of the fetus and internal podalic version.

6. Blood transfusions are invaluable aids in combating acute anemia and shock and in shortening the period of convalescence. Suitable donors for all suspected cases should be available at the time of delivery. Transfusions should be more frequently resorted to.

7. References are made regarding the frequency of placenta previa, the incidence of the various types of previas, parity, the period of gestation and the presentation and lie of the fetus.

8. As these cases were almost wholly taken from reports of leading obstetricians and maternity centers throughout the world the resulting statistics do not give an accurate picture of the results obtained in general practice. It is fair to assume that the mortality rates in general practice would be much higher than in maternity hospital practice.

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DISCUSSION

DR. IRVING F. STEIN, Chicago.—In a large proportion of our cases at Michael Reese Hospital simple puncture of the membranes has been one procedure which has been most successful. I cannot resist at this point to call attention to the little ring we have developed at Michael Reese Hospital which we facetiously call the "midwife's fingernail." To rupture the membranes, it is only necessary to flex the finger which releases the notched projection. It can be placed on the gloved finger for any vaginal examination, so in case the membranes should need to be ruptured, it is handy and a second introduction of an instrument is not needed.

In complete previa, particularly in a primipara, cesarean section should be done. Dr. Findley has shown a reduction in mortality with the low cervical section. We have never used the Latzko operation. We have had no deaths after low cervical section in primiparas at term or before term.

Bags are not used by us as a means of delivery, but when podalic version is indicated a bag may be introduced as a preparatory measure. We find ourselves using bags less and less, however. After the bag is out spontaneous delivery may occur, or forceps may be used if the head comes into the pelvis, or podalic version may be done.

In our clinic at Michael Reese Hospital we have practically abandoned Braxton Hicks version.

Accouchement forcé which was responsible in the past for the most serious complications, is now recognized as a distinct menace, and I think should be considered as malpractice.

Packing before delivery, I believe, should only be done when the patient is at home, and has to be transported after severe hemorrhage.

Transfusion is the most valuable adjunct to treatment instituted in recent years. In our hands transfusion by the syringe method has been preferable to the citrate method, though we are doing more and more citrate transfusions. However, reactions are more frequent than with the direct method.

DR. RUDOLPH W. HOLMES, Chicago.—We cannot determine the true incidence of placenta previa until we have the statistics upon all births with their complications in large communities, better whole countries. Hospital figures are not the indices of the prevalence of previa, for the rate here is necessarily much higher than at large. I have the records of 249 hospitals in which the average rate for placenta previa was 0.67 per cent. One small hospital had 9 per cent of their deliveries with this complication, and from this point the rates decreased until in one hospital there was but one previa in 2,174 deliveries. The maternal death rate in this series was 9.07 per cent, the fetal death rate 38.57 per cent.

DR. WALTER W. WELLS, Oklahoma City, Okla.—In the state of Oklahoma during the year 1936, there were 49,973 deliveries and 159 deaths, 28 of which were from uterine hemorrhage and 7 of these were placenta previa. At the University Hospital for the period from 1927 to 1937 there were 3,764 deliveries with 44 cases of placenta previa. Eight of these cases of placenta previa were placenta previa centralis. There were 22 bag inductions, seven of which were followed by version. Two patients were delivered by cesarean section. There were 17 fetal deaths

and one maternal death. At St. Anthony's Hospital during the same period there were 8,653 deliveries. There were 53 placenta previas, including 10 central placenta previas. Eleven patients were delivered by cesarean section. There were 1 quinine-castor oil induction, 3 versions, and 2 low forceps, 2 of which were followed by transfusion. There were 5 fetal deaths compared with 17 in the University Hospital, and 1 maternal death. The total number of placenta previas reviewed were 97.

Low cervical cesarean section is the operation of choice. In a primipara with undilated cervix and marginal placenta previa, cesarean section should be done. We make it a rule at the University Hospital that no patients with placenta previa leave the hospital undelivered.

AN ANALYSIS OF A HUMAN OVOTESTIS

Associated With a Congenitally Bisected Uterus Herniated into the Inguinal Canals*

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Memphis, Tenn.

INTRODUCTION

THE combination of unusual features associated with the malformations constituting the basis of this study are of such unusual excellence that no report of similar conditions has been found in the literature. Ovotestis is not rare and the fact that it is often associated with true or spurious hermaphroditism is likewise well known. Various shades or degrees of anomalies have been classed under the heading hermaphroditism, sometimes loosely and sometimes with careful and detailed analyses. The term "ovotestis" is used here to express specifically a gonad in which are commingled the biologic elements of both ovary and testis in varying proportions which may be either congenitally acquired or the result of faulty development embryologically.

CASE REPORT

The anatomic material furnishing the basis of this study was obtained from a white woman aged 39, who complained that she had never menstruated and at times suffered from severe tenderness in both inguinal regions since the age of 14. Her weight in the past seven years had increased from 98 to 134. The first of her 2 brothers had three children and the second the same number. Four of her 8 sisters are now living, the first of which has 4, and the second 7 children. The third sister has no children but seems to have enjoyed a normal sexual experience while the fourth sister had the same external defects as the patient. Of the dead sisters one died at the age of 49 after having had 10 children, the second died at the age of 16 from the effects of asthma, the third and fourth in infancy.

The physical examination revealed the external appearance of a female normal in stature, voice, and hair line. The normal and feminine appearing breasts became congested at irregular intervals. The abdomen was moderately obese. Bilateral masses, the size of an almond, rested in each inguinal region that were quite tender to the touch.

The vagina was shallow but no cervix could be felt or detected and nothing could be palpated in the pelvis. As a result of the physical examination, it was determined

*Read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

that the patient had a congenital absence of the uterus, associated with congenital abnormalities of the generative tract, bilateral inguinal hernia and mitral heart disease.

She was operated upon June 7, 1935, for bilateral hernia. Both canals were opened, and the masses in both sacs which were adherent to the sac walls were removed. One-half of the uterus was found in each sac along with part of the round ligament, the ovary and the blood vessels. The masses were removed by ligation, the sacs ligated also and the operative route closed by the Bassini method. Associated with the bilateral inguinal hernia, the operation showed that there was present also a congenital prolapse of the ovaries, rudimentary tube, and bisected uterus. The operation, in addition to the bilateral herniotomy, included a bilateral salpingo-oophorohysterectomy.

Gross Anatomy.—The two masses, one removed from the right, the other from the left, groin, presented a smooth peritoneal surface that faced the pelvic cavity and a rough adventitious coat that was embedded in the canal. Over the top of each mass there ran a portion of the round ligament and the degenerated oviduct which ended in a well-developed fimbria but in which no lumen could be sounded with a probe. The small gonads were hard and firm beneath which the broad ligament could be recognized. The uterine portion, one-half of which was associated with each gonad, was hard and infantile in appearance. Roughly each mass was a mirror image of the other indicating that the bilateral components had failed to meet in the median line, and hence, from some unknown period in embryonic development, the bilateral parts of the Müllerian system had pursued independent lines of development and produced bilateral halves of the uterus that eventually descended into the pelvic wall. Inasmuch as the vagina ended blindly, but was otherwise normal in structure, it must be inferred that it and the uterus arose from different and unconnected anlagen, which normally unite and break down to form the functional reproductive system of the female and this observation necessitates a modification of the view that the Müllerian system of the embryo gives rise to the female genitalia as far caudad as the hymen.

The uterine portion of the specimen was composed of a fundus and a body which descended into the pelvic wall where its identity was lost without giving rise to a recognizable cervix. The uterine portion, when examined histologically, was found to be composed of heavy connective tissue strands in abundance which were commingled with sparse and widely scattered smooth muscle strands, so jumbled in arrangement that definite configurations could not be determined. The epithelium was reduced to irregular and intermittent portions of tubules, associated with which were mere suggestions of glands, but in no place could glandular material be seen to suggest any glandular activity nor was the arrangement indicative that a continuous cavity ever existed in the center of the disordered uterus.

The elongated rod which ran over the gonad from the fundus of the uterus forward ended in a membranous fimbria but without an ostium. Sections of the tube revealed an intermittent epithelial lining around short cavities, suggesting that an attempt had been made to form a continuous lumen, but nothing suggested that any such continuous lumen had ever been achieved. Scattered smooth muscle cells were found in the walls haphazardly associated with exaggeratedly developed connective tissue strands that rendered the tube hard and firm. The round ligament was short and difficult to recognize, but the broad ligament was normal in structure, small and attached along the side of each bisected half of the uterus.

Gonads.—The difference in size of the right and left gonads was slight. The right one measured, including the tough fibrous capsule, tunica albuginia, 28.2 by 18.9 by 15 mm. and the left 27 by 13 by 12 mm. The capsule was 2 mm. thick, so that the measurements of the actual gonadal tissue were 24.2 by 14.9 by 11 mm., right and 23 by 9 by 8 mm. left.

Upon section of each gonad the cut surface revealed the presence of coarse and fine granulations among which were small white spherules that could be picked up and teased out with needles whereupon they would break off and float away in the dissecting fluid. Some of them were elongated and so twisted that they resembled the contorted tubules of the testis. Interlaced about the tubules were fine white

fibers that seemed to hold them in place. Nothing about the gross appearance of the gonad suggested its sex. Fibrous tissue penetrated into the stroma of the gonad after the manner of trabeculae and definitely delimited areas of different consistency. The areas of varying consistency were equally distributed throughout the gland, but the spherules and contorted tubular structures occupied much less space.

In thick sections (60 micra) under low power magnification (30 diameters), the contrasting areas offered different reactions to the stain. Some portions stained very darkly and others stained very lightly. The darkly staining areas were irregular in outline, and constituted a definite cortex that encroached with varying depths upon the medulla, which in general took the lighter stain. The lightly staining medulla radiated outward to end against the thick tunica albuginea and often to branch two or three times while doing so. Interlaced through the lighter streaks were strands of connective tissue fibers. The fibers were coarse and straight, the cells small, ellipsoidal and often indefinitely outlined. In various places, nodular masses of 2 to 3 mm. in diameter were encapsulated by the connective tissue fibers, which upon closer examination proved to be testicular in nature, while the diffuse, darkly staining cells, not so definitely encapsulated proved to be ovarian masses. The darkly staining gonogenic tissue showed regional differentiation toward ovarian and testicular materials in the ratio of 3 (ovarian) to 1 (testicular).

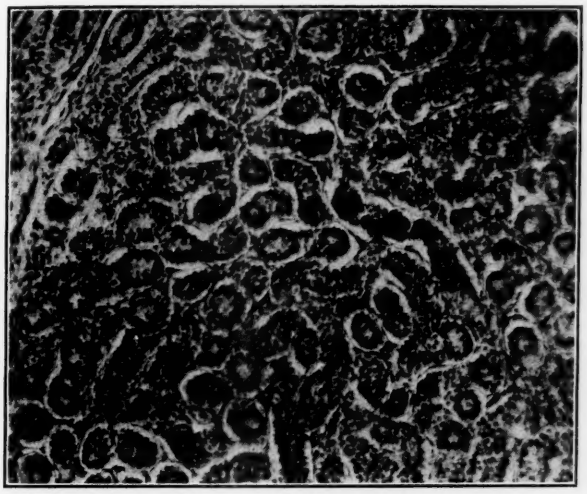

Fig. 1.—Testicular stroma of the ovotestis showing the tubules. ×260.

Testicular Material: The areas in which testicular material predominated were small and confined to the medullary portion of the cortical zone. The diameter of these spherules and tubules varied from 15 micra to 50 micra. For the most part all sizes were definitely delimited and surrounded by well-formed connective tissue capsules. In the smaller ones the connective tissue was quite thin but in the larger tubules it constituted a definite envelope (Fig. 1). Each testicular area was made up of these tubules which were short, contorted and possessed a definite basement membrane, not always seen clearly in connection with the small tubules, 20 micra or less. Supporting the larger tubules, 50 micra, the basement membrane was clearly visible on account of the inner cells having shrunken away from its inner surface. The cells within the larger tubules which may be likened to the spermatogonia were never more than two layers thick, often they were vesicular, and placed around a central space free from cells not unlike the lumen of a normal, embryonic tubule. It is in this space, or lumen where spermatids form and metamorphose into spermatozoa, but no cells approaching spermatogonia of the second order could be found, nor were there any indications anywhere that spermatids had ever been proliferated.

The interstitial material was scanty and no vacuoles or inclusions of any kind could be discerned in the cytoplasm of such cells. The appearance of the tubules, even those measuring 55 micra in diameter, was characteristically embryonic and rudimentary and showed a stage of differentiation attained by the normal testicle at the sixth month of gestation. In no cell was there ever seen any indication of mitotic activity, so that growth in size of the testicular portion was impossible.

Ovarian Material: The ovarian part of the gonad, about three times more extensive than the testicular and much more diffuse, contained a number of degenerating follicles in various stages of disintegration. In none could a true ovum be found, even in the smaller and more primitive follicles that departed least from the normal. The granulosa cells were thinly arranged about the periphery of the follicle, some of them lying loosely in the spaces ordinarily occupied by the liquor folliculi. Small clusters of cells were often met with in the central portions of the follicles leading one to think of them as fragmented ova in advanced stages of dissolution. Often a slight layer of ellipsoidal nuclei surrounded the follicles, the only recognizable remains of the theca interna (Fig. 2).

Fig. 2.

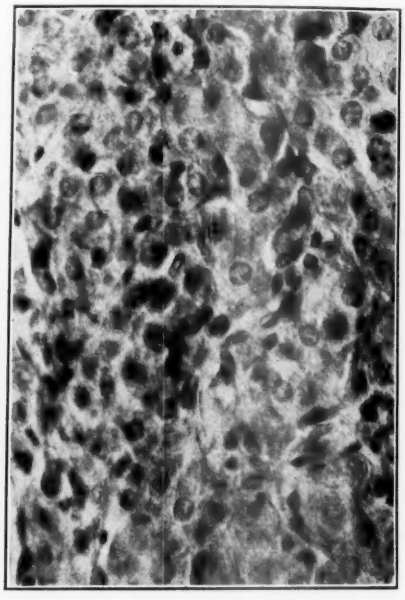

Fig. 3.

Fig. 2.—Ovarian mass of the ovotestis. ×260.
Fig. 3.—Ovarian portion of the ovotestis showing the genitaloid cells. ×736.

Associated with the degenerate follicles and lying in the same tissue with them are to be found the areas of diffuse ovarian stroma whose cells, for the most part, are large spherical elements closely recalling the genatoloid cells of the early fetal gonad. These large cells are somewhat vesicular (Fig. 3); the contained cytoplasm, without definite delimiting membranes, contains no conspicuous granules, no vacuoles, and unite diffusely with neighboring cells like them. The ovarian tissue, like the testicular, has attained the differentiation characteristic of a normal fetal ovary of the sixth month.

In neither the testicular nor the ovarian portions were the interstitial cells developed to an excess nor had the cells achieved the structure so characteristic of the specimens described by Jordan and Whitehead. Cells described by them as occurring in their specimens were not found in this one at all. In any case the importance of the interstitial cell as a source of the sex hormone can easily be over-

emphasized since the male or female sex hormone is not present to any great amount in the total absence of germinal material, that is, in the absence of follicles and seminiferous tubules.

Elsewhere, Simkins[3] has called attention to the fact that the ovary is essentially a cortical, and the testis a medullary gland, whose components do not run a course in development that are strictly synchronous. The ovary arises first and develops in such a manner as not to encroach upon the testicular portion which begins its development later, and differentiates out of a blastema that is not identical with, but is in close association with the ovarian anlage. It would seem then, that the embryologic factors governing the differentiation of the gonads are by no means antagonistic but follow an orderly series of events. The testis differentiating later than the ovary and arising from material adjacent to it, which gradually encroaches upon the ovarian cortex and replaces it with testicular tissue rather than by converting the ovarian blastema into testicular elements. The primary differentiation of the gonad, forming its embryonic fundament, the so-called indifferent gland is, from this point of view, essentially ovarian stroma, which if not interfered with leads to female somatic differentiation. The "interference" at the end of the so-called "indifferent period" is not a parting of the ways at the crossroads, but a progressive differentiation which if advancing leads to maleness, and if not, to femaleness. Forward gonogenesis produces the testicle at a later date and as a direct result of continued female differentiation, by a process of replacement, rather than conversion, in which the linear factor of time plays an important role.

Speemann's organ formers exert their influence upon the early differentiation of the sexual anlage, but what influence they may exert upon the subsequent sexual differentiation can only be conjectured. The doctrine that sex determination and differentiation depends upon a chromosomal basis has been arrived at by a consideration of the end result rather than by noting the influence of the male and female sex chromosome upon the organism during the process of sex differentiation. The influence of the sex chromosome may be profoundly altered by the cytoplasm around it in which the hormones may be present and to which it must react. A strict chromosomal regimentation may have to be modified in the light of hormonal determiners which may work in harmony with the genes of sex and to some extent modify or control their influence.

The notion of linear differentiation is strengthened by the effects of injections of male and female hormones upon the lower animals. Wiesner[4] has shown that female differentiation can, and does, go on in the absence of the female sex hormone. This lends support to the embryologic observation that if there is no interference with the embryologic development of the gonad it will first become an ovary. Of course we would expect, and we do find that female differentiation goes on, but to no decided extent when the female hormone is present, but the presence of the female hormone is not absolutely necessary for female differentiation.

On the other hand, however, the male hormone is necessary for male somatic differentiation. Even in the presence of the female hormone the male hormone forces the individual organism toward maleness, because the female hormone is superseded by the male. The immature gonads if stimulated by both male and female hormones progress toward male somatic differentiation and the ovarian tissue of the gonad is gradually replaced by testicular tissue.

The results of extensive experiments by Wiesner have prompted him to discard the dihormonic theory of sex causation and accept a monohormonic basis. His work, supported by that of Moore and Price, goes on to show that estrin, even if antiorchidic, is not a direct feminizer, and hence, is not concerned with female differentiation somatically. The male sex hormone is not so much antagonistic to female differentiation, but rather that it supersedes the inherent tendency of the organism towards female differentiation and forces it out and on beyond the female limits into the category of the male.

The testis hormone has no effect upon spayed females, but it does prevent the appearance of castration effects in males. Estrin does not hasten the involution of male sex characters when given to castrates, but when given in excessive amounts to normal males damages the testes and accessory organs. If both estrin and the male sex hormone are given at the same time the damaging effects of estrin are halted. The clitoris enlarges under the influence of androkinin (male sex hormone), but if thelykinin is given at the same time it fails to halt the masculinizing effect of the former, which indicates that the growth of the external genitalia is superseded by the male hormone. Thelykinin exerts a hysterotropic effect which is not retarded by androkinin. Somatic differentiation seems to be fundamentally female in the absence of any hormone at all, and that female differentiation takes place with or without the female sex hormone, but male characteristics are brought forth only under the influence of the male hormone. The cause of sex intergrades then, when explained upon such a basis would seem to lie in the effect of the stimulation of the soma by one hormone, the male. In the embryo this takes place whether the female sex hormone is present or not since the ovary is not necessary for female differentiation.

CONCLUSIONS

1. An unusual case of human ovotestis associated with a bisected uterus herniated into the inguinal canal has been described and analyzed.

2. Unique features are: the presence in each canal of a bisected uterus, fimbriated tubes, broad ligaments, and ovotestis.

3. The ovotestis was composed of ovarian and testicular tissue in the ratio of 3 to 1 (testicular).

4. Differentiation of the gonad had not gone on beyond the fetal period.

5. An explanation is offered for the cause of sex intergrades having its basis upon a monohormonic rather than a dihormonic system and that in the present case the male hormone was not powerful enough to force the embryologic development of the gonad completely out of the female or ovarian stage of differentiation into the complete somatic male.

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INTRALIGAMENTARY PREGNANCY

A Survey of All Published Cases of Over Seven Calendar Months, With the Discussion of an Additional Case

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IN THE fall of 1936, one of us (N. J. T.) operated upon a 39-year-old colored female for an intraligamentary pregnancy of eight and one-half months. The infrequency of this tumor warranted publication. The last investigation of this subject was by Remzy[37] in 1923. Unfortunately, he did not bring the literature up to date. We therefore attempted a complete survey and have recorded, according to year, in chart form all the cases reported.

The first article referring to intraligamentary pregnancy was by a German, Loschge[1] in 1816. He gave a beautiful detailed account of the autopsy findings of a young woman who died from rupture of an intraligamentary pregnancy at five and one-half months. His description of the anatomic relationship of the ovisac to the surrounding structures was most accurate and showed conclusively that this extrauterine pregnancy was developing in the broad ligament. Lawson Tait,[85] in his treatise on ectopic pregnancy in the late nineteenth century, convinced the medical profession of the possibility of this entity and in the year 1880 simultaneously with Maltakowsky[95] published reports of full-term intraligamentary pregnancies. In the following decade many additions were made. Sittner[70] in 1901 reported a series of 184 abdominal pregnancies, 39 of which were intraligamentary. Lemercier,[63] for his thesis, presented one case and added 18. Rosenblatt[59] in 1923 reviewed the literature from 1910 and out of 86 abdominal pregnancies, found 11 that were intraligamentary. One year later, Remzy[37] studied 30 cases in detail, placing particular emphasis on the disposal of the placenta. He was unable to reach any definite conclusions but stated that if possible the ovisac and placenta should be removed; however, conditions existing in the abdomen at the time of operation may alter the procedure. All these series contained many duplications which was fortunate, as Remzy's and Rosenblatt's abstracts frequently failed to afford us sufficient data. In spite of the duplications, and an earnest effort to locate the original articles, if the abstracts were scanty, the following cases could not be completed: Grimdale,[101] T. Wilson,[43] Ruder,[102] Immel,[59] and S. Fekete.[59] The original articles

of the latter two,[60, 68] were obtained but did not agree with the cases as abstracted from Rosenblatt's[59] series. Two references[51, 105] we were never able to find.

Our references were obtained from the *Quarterly Cumulative Index Medicus*, the *Index Catalogue of the Library of the Surgeon General's Office* in Washington, the *Quarterly Cumulative Index*, and the *Index Medicus*. The bibliography of each article was then searched for any further references. We are indebted to the Library of the Louisiana State University Medical School for its untiring efforts in obtaining the journals. The Surgeon General's Library at Washington, the John Crerar Library, Chicago, the New York Academy of Medicine, and the Orleans Parish Medical Society Library were our main sources.

To the best of our knowledge we have recorded every intraligamentary pregnancy of over seven calendar months that has been published, and present an additional case. We trust we have not missed too many.

CASE REPORT

A colored female of 39 years was admitted to the hospital Sept. 28, 1936, complaining of a mass in her abdomen of one year's duration. Her general health had always been excellent. Three full-term, normal pregnancies, and one five-months' abortion (not induced). Menses began at twelve, lasted three days, and occurred every four weeks. April 12, 1935: menstruated at her normal time, but the flow continued for six weeks; associated was a dull, suprapubic ache that never was severe or sharp. In July, 1935, she noticed a mass in her lower abdomen, and as amenorrhea had been present since April, the patient assumed she was pregnant. In October fetal life was felt. Pregnancy continued uneventful until the first part of January, 1936, when in the middle of the night, the patient was awakened with severe pains in the mid-epigastrium. The doctor in attendance believed that she was in labor. However, after forty-eight hours the pains ceased. At this time the patient noticed unusual activity of the infant which continued for two or three weeks, at which time all movement ceased; and there was marked engorgement of the breasts with lactation. A month and a half later she menstruated for three days, but amenorrhea continued until three months prior to admission, when her menses returned, were monthly, normal in amount and duration. The mass remained stationary in size from January, 1936, until admission.

On admission the patient appeared in excellent health and had no complaints. Examination revealed a large mass in the abdomen which extended from the pubis to a point halfway between the umbilicus and xiphoid. It was globular, smooth, semicystic, not tender, clearly demarcated and apparently not attached to the anterior abdominal wall. Vaginal examination revealed that the uterus was pushed to the left-anterior and was intimately adherent to the mass.

Wassermann was strongly positive, urine negative, sedimentation rate of thirty-five minutes. Blood chemistry: Blood urea, 14 mg. per 100 c.c. of blood, sugar, 80 mg. per 100 c.c. of blood.

A preoperative diagnosis was made of full-term abdominal pregnancy with dead fetus versus ovarian cyst. The unusual and suggestive history strongly indicated an extrauterine pregnancy.

Under subarachnoid analgesia, the abdomen was opened in the midline, incision extending from the symphysis pubis up to and beyond the umbilicus. Inspection revealed many fine adhesions between the tumor mass and the omentum and parietal peritoneum anteriorly, and to the sigmoid posteriorly. These adhesions were separated without undue difficulty. The mass was doughy in consistency with various

firm areas and appeared to be arising from the right parietal wall of the pelvis. No plane of cleavage or demarcation existed between the mass and the uterus. As it appeared to be intraligamentary, it was believed that the easiest way to mobilize the tumor would be by removing the uterus retrograde and then separate the tumor from its attachment. The infundibulopelvic ligament on the left was

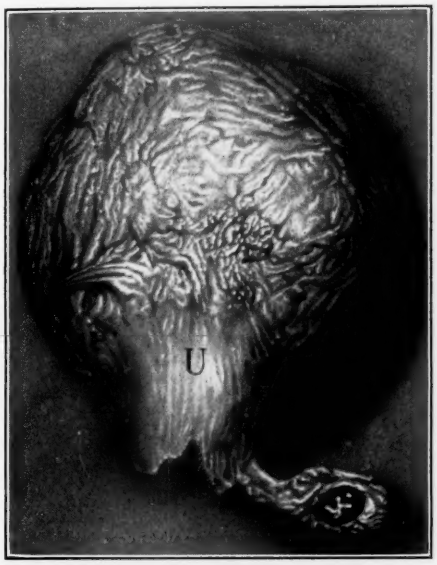

Fig. 1.—The left ovary, left tube, uterus, and broad ligament; the latter contain the ovisac before it was incised. This illustrates the continuity between the uterus and the tumor mass.

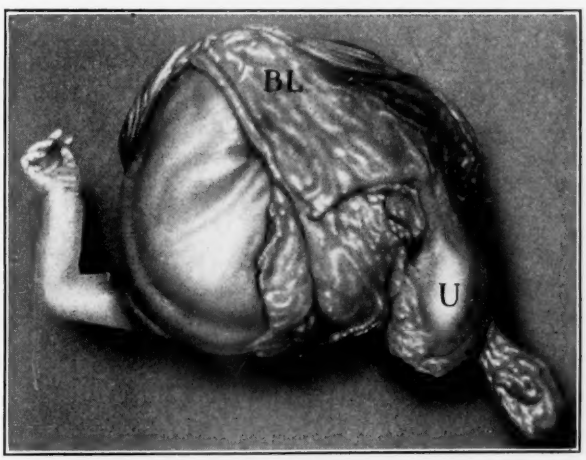

Fig. 2.—The fetus has been partially removed. *B.L.*, Broad ligament. *U*, Uterus.

therefore clamped and suture ligated, the broad ligament was severed in the avascular area down to the left uterine vessels which were clamped and severed. The uterus was then amputated at the level of the internal os and the right uterine vessels grasped and the entire mass with the uterus was then removed in toto. Some difficulty was encountered with the adhesions, but none with hemorrhage. The raw surfaces were peritonized with ease, utilizing the remaining portion of the broad

ligament and the uterine vesicle fold. On opening the sac, a macerated fetus was found which measured 43 cm. in length. The placenta was of the trilobate type, and covered the entire sac. The uterus was enlarged to twice the normal size and continuous with the mass. The uterine wall throughout was of equal thickness and no opening existed between the uterine cavity and the ovisac. No evidence of the tube or ovary on that side could be found in spite of many sections.

The postoperative course was uneventful and the patient was discharged on the twelfth day.

DISCUSSION

Of the four possible types of full-term extrauterine pregnancy only one seemed to apply to this case. None of the four criteria for ovarian pregnancy was present. Its location, mode of origin, and peculiar relation to the uterus eliminated abdominal and tubal pregnancy. The relationship of the ovisac to the uterus appears to us to be of paramount importance, the continuity of tissue being explained by remembering that the ovisac after rupture into the folds of the broad ligament will lie in loose areolar tissue, which is limited by the relatively dense folds of the broad ligament and its attachments. As growth continues, these folds are further and further separated and the ultimate boundaries are the attachments of the broad ligament, which are: the uterus medially, the lateral wall of the pelvis, inferiorly the pelvic floor, and superiorly the tube at which site rupture frequently occurs. It thus seems certain that any true intraligamentary pregnancy near term must have these boundaries and accordingly appear continuous with the uterus anterior and posterior as the folds and peritoneum of the broad ligament fuse with the fibrous covering and peritoneum of the uterus.

The main source of blood supply must necessarily spring from the blood vessels supplying the uterus and those in the base of the broad ligament. However, additional supply could arise from any structure which might lie adjacent to the developing ovum. The omentum and intestine, particularly the sigmoid, would be the most likely sources.

We feel thus that a diagnosis of intraligamentary pregnancy cannot be made if this peculiar relationship between the uterus and ovisac does not occur. An abdominal pregnancy that becomes implanted in the culdesac could present at term an almost identical picture except for its relationship to the uterus.

PATHOGENESIS

Until recently it has been assumed that this entity resulted from the rupture of the tubal pregnancy into the broad ligament. Granting that this is true, certain conditions must be fulfilled to permit an ovisac to become secondarily implanted in the folds of the broad ligament.

1. Implantation must occur in that portion of the tube that is uncovered by the peritoneum, permitting extrusion of the products of conception into the potential space between the folds of the broad ligament.

2. This rupture must occur early in the life of the embryo before the trophoblast has lost its power to insure secondary nidation. This action is rapidly lost as they are soon transformed into well-formed villi.

3. The interval between primary and secondary implantation must be of short duration or else death of the fetus will occur. Whether the extrusion of the ovisac from the tube into the broad ligament should be gradual or rapid to promote optimal conditions for secondary growth is difficult to say. However, in the cases we reviewed, the frequency with which we have encountered a history of prolonged lower abdominal pain in the early months of gestation leads us to believe that this passage is slow. This pain, however, could be caused by the adaption and stretching of the broad ligament to its new occupant and not to the rupture.

Roxas and Villarama[38] observed that the trophoblastic cells rapidly develop into chorionic villi and that once this change has occurred, disruption of the primary implantation will result in death of the embryo. Accordingly they believe that secondary implantation is impossible and that in intraligamentary pregnancy the blastodermic vesicle burrows through the peritoneum and fascia of the posterior fold of the broad ligament into this potential space, where the loose areolar tissue is conducive to further growth and development.

Frankel and Schenck[110] claim that endometrial tissue is a prerequisite to nidation. In their last article they state that in 14 out of 16 cases of ectopic pregnancies, endometrial tissue was present in the Fallopian tubes and explain their findings on the basis of Sampson's theory.

Believing that it is anatomically impossible for an ovisac measuring 5 or 6 cm. to rupture into the folds of the broad ligament, and that it is unlikely that a fertilized follicle would select for implantation the posterior layer of the broad ligament in preference to adjacent abdominal viscera or omentum, we think that a more plausible explanation of this phenomenon could be that this results from the development and growth into the folds of the broad ligament of a primary or secondary ovarian pregnancy, or a primary abdominal pregnancy implanted near this site, by the same mechanism that cysts of the ovary become intraligamentary.

We further believe that rarely is a full-term pregnancy or a large cyst completely enclosed in the folds of the broad ligament. As growth is rapid, thinning and attenuation of the broad ligament occurs so quickly that rupture is inevitable. This can account for the frequency of the many adhesions of the ovisac on its medial and superior border to adjacent viscera. Just recently we have encountered several very large ovarian cysts that were intraligamentary and over three-fourths of the cyst walls were covered only by a thin layer of peritoneum, the limits of the broad ligament being easily discernible. In many of the recorded cases mention was made of the inability to peritonize the wound. In true intraligamentary cysts or pregnancies this difficulty is never encountered as a peritonized broad ligament is in abundance.

TABLE I

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Loschge[1]	1816	5½	D	D		Autopsy revealed rupture of sac with intestinal hemorrhage. Description of anatomy typical of intraligamentary
Lawson Tait[85]	1880	9	L	D	Marsupialization	Death 4th day P.O., exhaustion
Maltakowsky[95]	1880	9	L	L	Partial removal of placenta, packed	Ureter clamped with subsequent nephrectomy
Breisky[87]	1887	8	L	L	Total removal of placenta	
Spaeth[88]	1888	8	L	D	Marsupialization and tamponade, amniotic fluid fetid	Death following day, septicemia. Fetus died 24 hours
Taotman[89]	1888	8	L	L	Removal of sac and placenta, packed, drained, severe hemorrhage	
Eastman[9]	1888	8	L	L	Removal of sac and placenta, drainage, glass drain	
Cullingworth[2]	1888	7½	D	L	Total removal of placenta	Fetus dead 8 months, macerated
Negri[71]	1898	8	L	L	Partial removal of placenta and sac, marsupialization	Fetus died from a malformation
Oliver[92]	1890	9	D	L	Marsupialization, amniotic fluid was purulent	Peritonitis. Fetus had been dead 5 months
Galabin[72]	1890	8	L	D	Marsupialization	Death second P.O. day, sepsis and hemorrhage
Voight[67]	1891	9	D	L	Total removal of placenta, partial marsupialization	
Schauta[98]	1891		D	L	Removal of sac and placenta	
Marchand[97]	1892	9	L	D	Marsupialization	Died following day. Autopsy showed bleeding from partially detached placenta
Rein[21]	1892	9	L	L	Total removal of placenta, drained with glass drain	
Frommel[91]	1892	8	L	L	Marsupialization and tamponade, profuse hemorrhage	Fecal fistula, closed spontaneously
Sippel[74]	1892	8½	L	D	Removal of sac and placenta	Death first day P.O., hemorrhage
Pan[100]	1893	9	L	L	Removal of sac and fetus	

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Lusk[75]	1893	7	D	L	Tamponade	
Hofmeier[76]	1893	9	D	L	Partial removal of placenta, marsupialization, tamponade	
Tauffer[73]	1893	7	D	L	S.V.H. with removal of sac and placenta	
Griffith[13]	1893	9	D	L	Removal of sac and placenta, drainage, glass drain	
Herff[77]	1895	8½	L	L	Removal of sac and placenta	Fever, thrombophlebitis
Hardie[78]	1896	8	D	L	Marsupialization	
Galabin[12]	1896	9	D	L	Removal of sac and placenta and ovarian tumor	Fetus dead 21 years and macerated. Braxton Hicks had diagnosed 21 years before
Dunning[7]	1897	8	D	L	Removal of sac and placenta	
Rokitansky[79]	1898	8½	L	L	Partial removal of placenta with tamponade	
Rochet[96]	1898	9	D	L	Evacuation of sac	Placenta removed 7th day P.O. Fetus macerated
Martin[18]	1899	8	D	D	Removal of pelvic organs in toto, drainage abdomen and vagina	Died, day? Fetus macerated
Donald[6]	1899	7	Died at O.R.	L	Packed. Fetus extracted by vagina	
Jayle, Delherm[16]	1900	9	D	L	Marsupialization	Fetus macerated, dead 7 months
Cragin[80]	1900	8	L	L	Tamponade	
Menge[81]	1900	8	D	L	S.V.H., removal of sac and placenta	
Boryssowicz[82]	1900	8	L	L	Marsupialization	Placenta removed 6 weeks P.O.
Cragin[83]	1900	8½	L	L	Removal of sac and placenta	
Lemercier[63]	1900	9	D	L	Marsupialization	Fetus dead 8 months and macerated
Sneguireff[84]	1900	8½	L	L	Partial removal of sac and placenta. Marsupialization. Tamponade	
Skutsch[86]	1902	7		L	Marsupialization, hemorrhaged and packed	
Lyle[17]	1906	9	D	L	Attempt made to remove placenta, unsuccessful	Fetus macerated, 18th P.O. day, colpotomy

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Rodiger[22]	1906	9	D	L	Packed with iodoform gauze	Fetus macerated
Tissier, Wiart[41]	1908	8	L	L	S.V.H., total removal of placenta, drainage	
Lobenstine[34]	1908	8	D	D	Total removal of placenta, packed, marsupialized	Died few hours P.O. hemorrhage and shock
Tissier, Penard[40]	1909	9	D	D	Marsupialization, uterus ruptured, cause?	Death following day. Fetus macerated
G. D. Nutt[61]	1910	9	D	L	S.V.H., removal of sac and placenta	Fetus macerated, dead 2 years
Gitelson[69]	1910	8½	D	D	Total removal of placenta, marsupialization, drainage	Died sixth day, P.O. peritonitis
Grimdale[101]	1910	9	D	L		
MacPherson[35]	1911	9	?	L	Hemorrhage prevented removal of placenta, packed	Phlebitis
Scipiades[39]	1911	9	D	L	Removal of sac and placenta	Fetus macerated
Velitz[66]	1911	8	D	L	S.V.H., total removal of placenta, resection of intestines	
Immel[59]	1912	9	L	L		
N. L. Hood[62]	1913	9	L	L	Partial removal of placenta, marsupialization, drainage	
S. Fekete[59]	1913	9	D	L		
T. Wilson[43]	1913	9	D			
Engelking[31]	1913	8	D	L	Removal of sac and placenta	Fetus macerated
Stoeckel[94]	1916	9	–	–	Total removal of placenta	Drained through cul-de-sac
Marriott[36]	1918	9	D	L	Total removal of placenta	Fetus macerated. Dead for 8 months
Kuncz[65]	1919	9	D	L	S.V.H., removal of sac and placenta	
Ruder[102]	1919	9	D	L		
Ellison[49]	1922	9	D	L	Total removal of placenta, no drainage	Sinus closed 100 days P.O.
Roxas, Villarama[38]	1924	9	L	L	Partial removal of placenta, abdominal drainage	
Remzy[37]	1924	7	D	L	Total removal of placenta, packed	Phlebitis, pulmonary embolus. Fetus macerated
Thompson[50]	1928	8½	D	L	Partial removal of placenta	Toxemia of pregnancy. Intestinal obstruction 2 mo. later

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Magid[52]	1928	8	D	L	Diagnosis of intraligamentary is questionable	Toxemia of pregnancy
McLennan[53]	1931	8	L	D	Removal of sac and placenta	Died 16 days P.O. peritonitis and nephritis
Ware[57]	1934	9	D	L	Partial removal of placenta, packed	P.O. sinus 6 wk. with temperature 4 weeks. Fetus macerated
Ware[57]	1934	9	D	L	Total removal of placenta, packed and marsupialized	Fetus macerated
Cernoevic[58]	1935	9	D	L	Total removal of placenta, packed, drained	
Tessitore, Champion	1936	8½	D	L	S.V.H., L.S.O., removal of sac and placenta, no drainage	Fetus macerated, dead 10 months
R. W. Hardy[99]	1937	8	D	L	Removal of sac and placenta. No drainage	Fetus calcified, dead 10 years
Toth[37]	Before 1924	9	–	–	Removal of sac and placenta	

INCIDENCE

We have previously described the structural relationship that we believe must exist between the body of the uterus and the ovisac before one is justified in arriving at the diagnosis of a broad ligament pregnancy. With several exceptions there is little reference in the operative procedure of the many cases reported that would enable one to study the literature from this angle. This is unfortunate from a statistical viewpoint and prohibits arriving at any conclusion regarding the true frequency of this entity. Kennedy[49] estimated that one out of every 613 cases of ectopic pregnancy is intraligamentary. He derives this ratio from the statistical reports of Sittner,[70] Rosenblatt,[59] Farrar,[106] Lewis,[107] Luker,[108] Mason and Storro,[109] and Williams.[104] It is generally accepted that ectopic pregnancy occurs about once in every 200 pregnancies and that the ratio of abortion to pregnancy is one to two. From these figures it may be estimated that out of every 183,900 pregnancies, one will be intraligamentary.

To facilitate the analyzing of the cases reported, we divided them into decades for comparison.

MATERNAL MORTALITY

The maternal mortality was 16 per cent (Table II) and showed a tendency to decrease with each decade. This is to be more or less

expected as operative technique and asepsis are improved. Of the 10 maternal deaths, 5 were due to hemorrhage. In 3 of the 5, a living child was obtained, the other 2 being dead, but not macerated. This association of hemorrhage with a living newborn is significant, and is to be remembered when an attempt is made to remove a placenta with evidence of bleeding from the placental site. In these cases it is much safer to evacuate the sac and close the abdomen. The placenta will be readily absorbed.

TABLE II. COMPARISON BY DECADES OF MATERNAL AND FETAL DEATHS

	1880 1889	1890 1899	1900 1909	1910 1919	1920 1929	1930 1937	TOTALS
Number of cases	8	21	13	10†	4*	6	62*†‡
Number of maternal deaths:	2	4	2	1	0	1	10‡ or 16%
Sepsis	1	1		1		1	4
Exhaustion	1						1
Hemorrhage		3	2				5
Number of fetal deaths:	1	13	7	7†	4	5	37†‡ or 58%
Macerated	1	4	5	4	1	4	19
Prematurity		3					3
Not stated		6	2	3	3	1	15

*Magid's case omitted.

†Five cases omitted as records incomplete. Grimdale,[101] Immel,[50] S. Fekete,[50] T. Wilson,[43] Ruder.[102]

‡Cases of Loschge[1] and Toth[37] not included.

FETAL MORTALITY

The fetal mortality was 58 per cent and a little over half of the dead fetuses were macerated. In several cases the fetus had been retained with no apparent injury to the mother for many years; ten years in Hardy's case and twenty-one years in the case of Galabin. The latter is interesting as the patient had formerly been under the care of Braxton Hicks, and was diagnosed in 1872 as a full-term extrauterine pregnancy. Conservative therapy was advised, and twenty-one years later a rapidly growing ovarian cyst necessitated operation due to the pressure symptoms.

OPERATIVE PROCEDURES

The operative procedures (Table III) of tamponade and packing were isolated but probably belong under the same heading. It is also clear that it is impossible to pack without draining. Since 1910, the incidence of marsupialization has greatly diminished. In recent years, if the ovisac and placenta could not be removed the abdomen has generally been closed without packing or marsupialization. There has also been a tendency, however, to remove the placenta in every case. This is regrettable as the retained placenta is readily taken care of, and removal frequently produces an uncontrollable hemorrhage.

TABLE III. COMPARISON BY DECADES OF OPERATIVE PROCEDURES

	1880 1899	1890 1899	1900 1909	1910 1919	1920 1929	1930 1937	TOTALS
Number of cases	8	21	13	10†	4*	6	62*†‡
Operative procedures							
Marsupialization	3	7	7	2		1	20
Partial removal of placenta	2	2	1	1	2	1	9
Total removal of placenta	2	2	1	3	2	2	12
Tamponade	1	4	3				8
Removal of sac and placenta	2	7	1	2		2	14
Packed	2	1	3	1	1	3	11
Drained	2	3	1	2		1	9
Hysterectomy with removal of sac and placenta		2	2	3		1	8
Evacuation of sac		1	1				2
Resection of intestines				1			1
Total number of operative procedures	14	29	20	15	5	11	94

*Magid's case omitted.

†Five cases omitted as records incomplete. Grimdale,[101] Immel,[59] S. Fekete,[59] T. Wilson,[43] Ruder.[102]

‡Cases of Loschge[1] and Toth[37] not included.

DIAGNOSIS

The diagnosis of full-term extrauterine pregnancy has recently been excellently presented in papers on abdominal pregnancy, so we will not discuss this in detail. Recognition of this condition requires alertness on the part of the examiner, but a careful history and physical and vaginal examinations under general anesthesia, if necessary, should enable one to recognize this entity in the majority of cases. In our patient the uterus could be palpated separate from the tumor. If the indications are present, exploration of the uterine cavity will clinch the diagnosis. An x-ray of the abdomen will demonstrate (1) a fetus which appears higher than normal, (2) faulty or no engagement, and (3) abnormal presentations.

TREATMENT

This depends upon the viability of the infant.

1. *Viable Fetus.*—Operation is indicated. Type of operation will vary with findings. Ideally, removal of the sac and placenta should be performed. If the placenta is attached to any viscera from which it cannot be readily freed or if it is evident that difficulty will be encountered with bleeding, the best results will be obtained if the placenta and sac are left in situ. If the mother has several children or has no desire for further progeny, or if it is technically difficult to remove the ovisac without the uterus, the latter may have to be sacrificed. If drainage is thought advisable, the vaginal route is preferable.

2. *Dead Fetus.*—With absence of infection, operation should be deferred until the fetal circulation has sufficiently atrophied that the danger of hemorrhage is reduced to a minimum. The length of time necessary to enable these retrogressive changes to occur is difficult to determine, due to paucity of material and limited experience of any

one operator with this entity. However, we feel six to eight weeks should be allowed to elapse, and no difficulty should then be encountered with hemorrhage in removing the sac and placenta. Dense adhesions to vital organs may likewise prevent complete removal, but this should not be encountered in intraligamentary pregnancy with the frequency found in abdominal cases.

CONCLUSIONS

1. An attempt was made to present a complete survey of the literature of the intraligamentary pregnancies of over seven calendar months with the discussion of an additional case.

2. The anatomic relationships necessary to diagnose an extrauterine pregnancy were discussed. Special emphasis was placed on the complete continuity of the uterus and the ovisac, anterior and posterior, and the absence of any line of demarcation.

3. Treatment was outlined. If the infant is viable, operation with conservative handling of the placenta is indicated. If the fetus is dead, operation should be deferred six to eight weeks until the placental circulation has atrophied.

4. A suggestion was made as to the origin of this type of pregnancy.

5. Intraligamentary pregnancies occur once in every 183,900 pregnancies.

We are indebted to Dr. Peter Graffagnino for his kind help and many valuable suggestions and to Dr. Charles Midlo, whose excellent cooperation in translating the publications of the German and allied tongues made this survey possible.

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OBSERVATIONS ON INTRAUTERINE PRESSURE DURING FIRST STAGE OF LABOR

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THE evaluation of intrauterine pressure has been a problem of much interest and much speculation. Most of the older observers have been content merely with attempts to determine the tension of the amniotic sac and the amount of expulsive force of the uterus, with the aid of the abdominal musculature. Accordingly, I have performed a number of experiments on patients in labor, making use of a Voorhees bag and a specially designed pressure recording apparatus. From these experiments I have compiled a series of tabulations and data which seem to me to be indicative of the true intrauterine pressure.

Poppel in 1863 thought that a study of the resistance of the fetal membranes would permit him to draw approximate conclusions with regard to the total pressure exerted by the uterine contractions on the uterine contents. Duncan in 1869 thought that the tensile strength of the amniotic membrane alone sufficed to give an indication of the amount of pressure necessary to rupture membranes.

A critical study of the work done by both of these men shows that neither one of them simulated or even approximated physiologic conditions. The membranes were firmly fixed to the margins of the vessels used and because of this the inherent elasticity of the membranes was not given free range as normally occurs. Both directed the testing force against a small area of membrane, and they were content to measure this force as representative of the true uterine pressure.

Schatz who was the first to use internal hysterography in the study of the dynamics of the uterus found the intrauterine pressure before the onset of labor and between the labor pains to be equal to 20 mm. of mercury. This pressure he called the pseudo intrauterine pressure. During labor pains the height of the column of mercury varied from 80 to 250 mm. of mercury. These readings were obtained throughout the course of an entire labor and no attempt was made to remove or account for the accessory forces which come into play during the second stage of labor and because of this, these readings are not indicative of a true intrauterine pressure.

Westermarck in 1893 showed that at the beginning of labor the pressure was about 20 mm. of mercury while at the height of the pain the pressure recorded varied greatly up to 168 mm. of mercury. His observations were carried through the second stage of labor.

Weilock, in a recent paper on the measurement of the pressure in the hydramniotic uterus, brought out conclusive data showing that in the normal pregnant uterus before the onset of labor the pressure is practically nil. His experiments were performed by inserting a cannula through the abdominal and uterine wall into the amniotic sac.

FORCES CONCERNED IN LABOR

As long as the membranes are unruptured during the first stage of labor, whatever force is exerted by the contracting musculature of the uterus is transmitted to the liquor amnii and by it to the fetus. In accordance with the laws of fluid pressure, it is transmitted equally in all directions and since the lower uterine segment and the cervix offer the least resistance we have a resultant stretching of the lower uterine segment and a dilatation of the cervix. If the above can be assumed to be true, there is no reason to believe that the fetus should exert pressure on the lower uterine segment, but if it does, it is not in excess of that exerted by the uterus on the amniotic fluid.

With regard to the pressure of the abdominal wall we may say that it exerts no pressure on the abdominal organs unless the abdominal musculature is voluntarily contracted. However, during labor, when the cervix has retracted and the presenting part lies on the perineal floor, the abdominal muscles reflexly come into play and the patient bears down. At this time, the expulsive force on the uterine contents is a combination of the uterine muscular contractions and the contractions of the abdominal musculature. Prior to this time and before the cervix is completely dilated, there is no tendency on the part of the patient to bear down unless she is so instructed by the attendant or else thinks that by bearing down she may hasten the completion of labor. From this it can be assumed that prior to complete dilatation or when the presenting part is on the perineum, the pressure exerted on the uterine contents is derived exclusively from the uterine musculature during their contractions. To attempt to differentiate just how much is due to accessory muscle action is a problem worthy of consideration.

In the series of cases presented in this paper, all of which except one were full term, a large Voorhees' bag was inserted into the uterus prior to the onset of labor and then the bag was filled with approximately 800 c.c. of a 1:3,000 bichloride solution. The diameter of the base of the bag was 11 cm. The presenting part was kept out of the pelvis until the cervix was completely dilated by the size of the bag. In all cases care was taken not to rupture the amniotic sac. The free end of the Voorhees bag was then connected to a specially constructed manometer and readings were taken from the beginning of labor until complete dilatation of the cervix. The introduction of the bag into the uterus and its subsequent filling with bichloride solution itself created a pressure, then again the increase in uterine contents served to increase the pressure inside the uterus. The pressure so created has been designated the standing uterine pressure. The difference in pressure between the standing pressure and the pressure obtained during a uterine contraction has been designated the relative intrauterine pressure.

DESCRIPTION OF APPARATUS

The apparatus consists of a stand with a mercury manometer (Fig. 1). The manometer is so fixed that it can be raised or lowered according to the level of the Voorhees' bag inserted in the uterus. Fluid is forced out of the bag in accordance with the amount of pressure exerted. This in turn is transmitted through a column of air to a column of mercury on a millimeter scale. The difference in the level of the column of mercury is taken as a measure of the force of the uterine contraction.

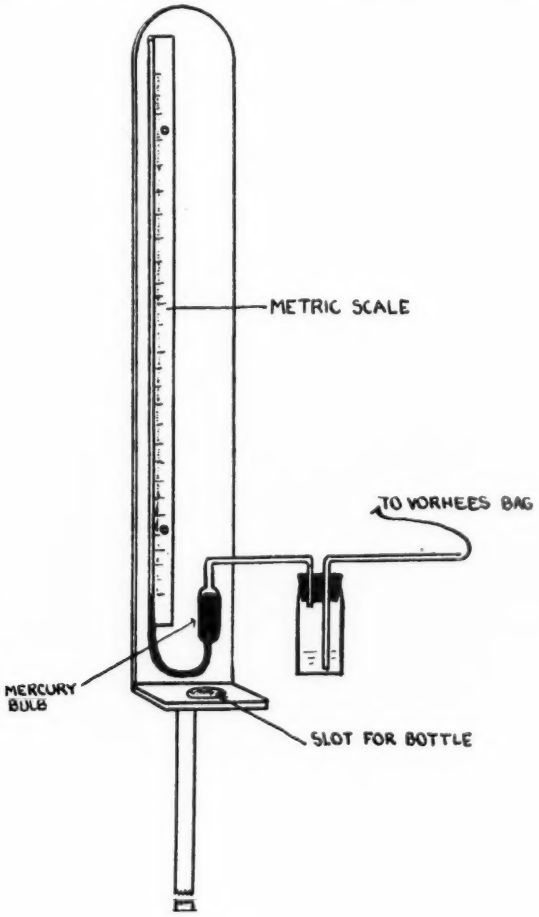

Fig. 1.

CONSIDERATION OF CASES

In the selection of cases for the determination of the intrauterine pressure, only those patients were selected in whom there was no contraindication to the insertion of the Voorhees' bag. Labor was allowed to occur spontaneously, no traction was applied to the bag in order that the lower uterine segment would not be thinned out except by pressure exerted by the uterine contractions. The record-

ings began at the onset of labor and were continued throughout until complete dilatation of the cervix occurred. Frequent rectal examinations were made to determine when the cervix was completely dilated. As soon as this occurred, the fluid was allowed to drain out and the bag removed. In one case the bag was allowed to be expelled by the uterus and accessory forces in order that a comparison might be drawn between intrauterine pressure and pressure exerted by the abdominal musculature in the process of bearing down.

PRESENTATION OF DATA

Presentation of each case in detail is impractical, therefore several will be presented in graph form, as the entire course of labor during the first stage can be graphically represented. Other cases will be presented in chart form.

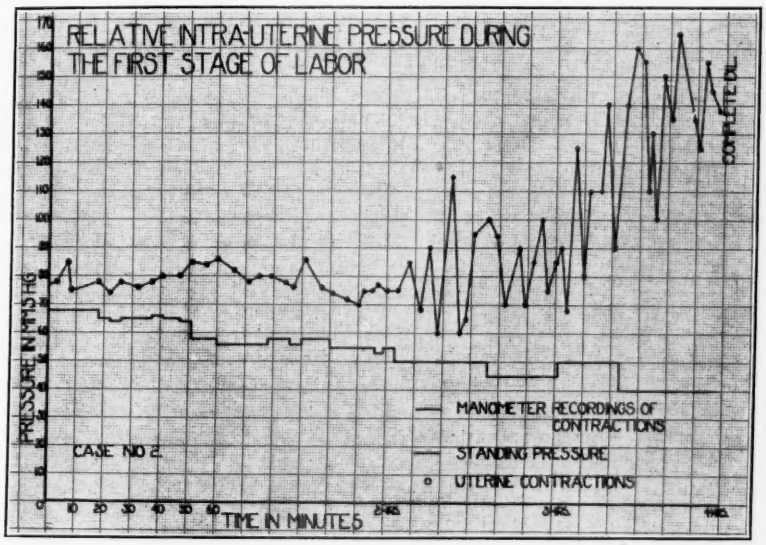

Fig. 2.

The graph of Case 2, a primipara, shows the elevations of the mercury manometer readings over the standard pressure readings for each pain (Fig. 2). The time of onset of each contraction in relation to the previous as well as to the following contraction is also shown. From the graph it will be clearly seen that as the first stage of labor nears completion the relative intrauterine pressure values increase, while the standard pressure values decrease as the first stage nears completion. The decrease in standing pressure is explained by the fact that as the first stage of labor nears completion the Voorhees' bag is gradually being pushed out of the cervix thus decreasing the uterine contents.

This case was selected because it showed the maximum value of relative pressure obtained in the series. During the course of delivery all the amniotic fluid was collected in a basin and the volume measured. In this case the volume was 470 c.c. The placenta and membranes were measured according to the volume of water which they displaced and were found to be 500 c.c. In a similar manner the fetus, ex-

cepting the nose and mouth, was immersed in a basin of water and the volume of fluid displaced measured, which in this case was 2,900 c.c. Thus, the total volume of the uterine cavity was found to be 3,950 c.c.

All the remaining cases have been handled in the same manner; the data obtained tabulated and recorded in chart form. Case 1 in Table I corresponds to Case 1 in Table II, etc.

TABLE I. LENGTH OF LABOR WITH BAG INDUCTION

CASE	AGE	PARA	McDONALD CM.	CERVIX		INSERTION OF BAG	ONSET OF LABOR AFTER INSERTION OF BAG	LENGTH OF LABOR
				DILATATION CM.	THICKNESS CM.			
1	21	i	35	3.0	0.5	11:45 A.M.	4 hr. 45 min.	2 hr. 20 min.
2	21	i	33	2.5	0.5	12:00 M.	1 hr. 19 min.	4 hr. 3 min.
3	18	i	34	2.0	1.0	10:30 A.M.	2 hr. 30 min.	8 hr. 30 min.
4	26	vi	31	2.5	0.5	10:30 A.M.	2 hr. 15 min.	2 hr. 25 min.
5	30	v	39	2.5	1.0	2:30 P.M.	1 hr. 56 min.	2 hr. 15 min.
6	22	i	35	2.0	0.5	9:45 A.M.	9 hr. 41 min.	5 hr. 4 min.
7	23	i	29	2.5	1.0	9:30 A.M.	2 hr. 55 min.	13 hr. 45 min.
8	20	i	36	3.0	1.0	10:00 A.M.	3 hr. 35 min.	3 hr. 57 min.
9	19	i	36	2.5	1.0	10:30 A.M.	2 hr. 10 min.	5 hr. 24 min.
10	19	i	36	2.5	1.0	10:00 A.M.	3 hr. 30 min.	5 hr. 50 min.
11	18	i	33	2.0	1.0	1:15 P.M.	4 hr. 7 min.	4 hr. 54 min.

TABLE II. RELATION OF PRESSURE TO VOLUME OF UTERUS AND NUMBER OF PAINS

CASE	VOLUME OF FETUS C.C.	VOLUME OF PLACENTA C.C.	VOLUME OF FLUID C.C.	TOTAL VOLUME C.C.	LENGTH OF LABOR	NUMBER OF PAINS	MAXIMUM PRESSURE MM.	MINIMUM PRESSURE MM.	AVERAGE PRESSURE MM.
1	3025	575	555	4155	2 hr. 20 min.	37	92	12	41.3
2	2900	580	470	3950	4 hr. 3 min.	75	125	8	43.3
3	3775	650	600	5025	8 hr. 30 min.	195	80	7	24.6
4	2300	470	395	3165	2 hr. 25 min.	85	65	9	23.1
5	3000	550	480	4030	2 hr. 15 min.	48	45	10	22.3
6	3300	510	455	4265	5 hr. 4 min.	153	50	10	28.7
7	2100	250	435	2785	13 hr. 45 min.	164	54	13	35.4
8	4050	750	850	5650	3 hr. 57 min.	104	43	8	23.2
9	4000	690	350	5040	5 hr. 24 min.	70	47	11	31.7
10	2300	525	610	3435	5 hr. 5 min.	139	72	9	27.6
11	2750	500	525	3775	4 hr. 54 min.	58	75	12	49.9

By a careful study of the tables, it can be seen that the duration of labor in all these cases, with the exception of one case, was much shorter than in the average spontaneous case. Only the first stage of labor is being studied. Attention is directed to this fact because the pressure created by the uterus should be greater if the duration of labor is shorter than normal. The time required to dilate the cervix is taken as a criterion of the greater pressure in the shorter labor. As a matter of interest and that there may be a basis of comparison, two multiparous patients were used in our experiments. These are represented in the tables as Cases 4 and 5. The average duration of labor in the primiparous patients was four hours and fifty-one minutes; in the multiparous patients it was two hours and twenty minutes.

Table II presents data relating to the volume of the uterus, the length of the labor, and the number of pains in comparison to the average relative pressure values obtained during the course of the first stage of labor. This chart brings out the fact that the volume of the uterus is not related to the number of pains nor to the length

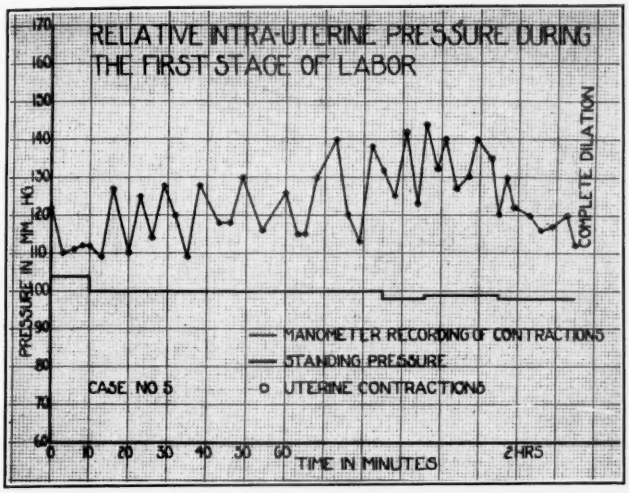

Fig. 3.

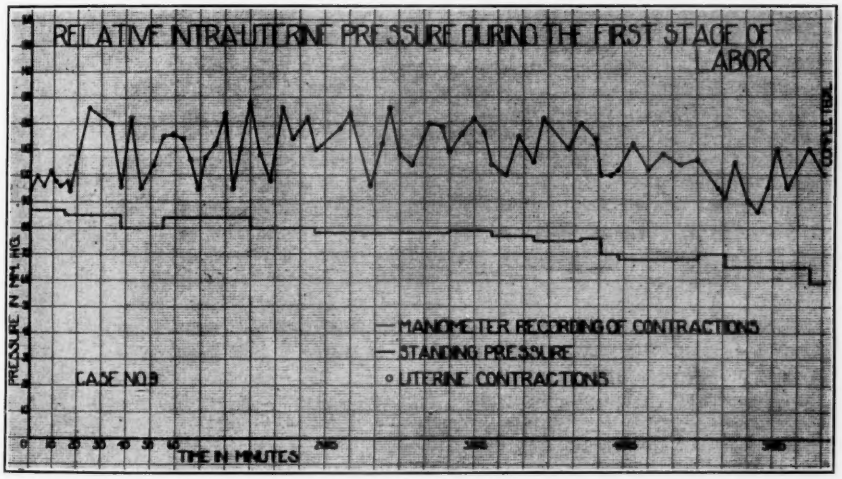

Fig. 4.

of the labor. It shows rather conclusively that in those labors with fewer pains during the first stage, the average relative pressure values obtained were greater. This is true of the primiparous patients only, as in the two cases of multiparas, the average relative pressure values were the lowest in the series even though the average length of those labors was only two hours and twenty minutes.

The graph of Case 5 (Fig. 3), a multipara, shows that the duration of the first stage of labor is much shorter and that the relative pressure values are not as great as in the primipara.

The graph of Case 9 (Fig. 4) represents the case in which the membranes were ruptured purposely in order to note the effect on relative pressure values. It will be seen here that the contractions seem to maintain approximately the same intensity throughout the entire first stage of labor. Whether this was due to the fact that the membranes were ruptured or whether it was just a peculiarity of this particular case was not determined.

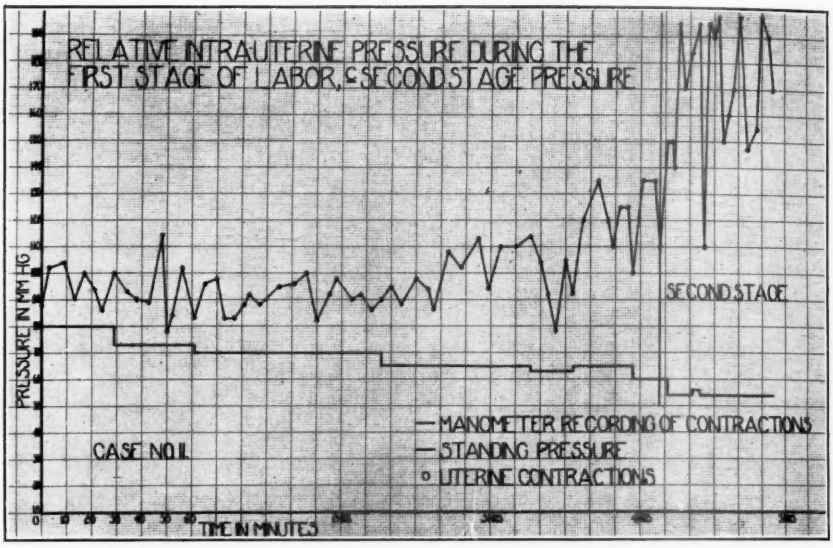
RELATIVE INTRA-UTERINE PRESSURE DURING THE FIRST STAGE OF LABOR, & SECOND STAGE PRESSURE
SECOND STAGE
PRESSURE IN MM HG
TIME IN MINUTES
CASE NO. 11
— MANOMETER RECORDING OF CONTRACTIONS
— STANDING PRESSURE
o UTERINE CONTRACTIONS

Fig. 5.

The graph of Case 11 (Fig. 5), a primipara, is the one in which the Voorhees' bag was allowed to remain in the vagina throughout the second stage of labor, so as to show more clearly the greater pressure exerted during the second stage.

OBSERVATIONS OTHER THAN THOSE DEALING WITH THE PLAN OF WORK

The use of the Voorhees' bag has made possible certain incidental observations on the effects of the intrauterine bag on uterine contractions and the course of labor.

Normally, in the beginning of spontaneous labor the contractions are usually weak and irregular. In this series of cases, the period of weak and irregular contractions has been markedly shortened, hence the duration of the first stage of labor has been shortened in almost all of these cases.

The character of the contractions in this series also shows some interesting features. The time from the onset of the contraction up

to the time when it reaches its maximum was very short, varying from fourteen to eighteen seconds. The contraction was maintained at its peak for four to eight seconds and then there was a gradual fall to the standing pressure. This last phase of contraction was longest, lasting from twenty-two to twenty-eight seconds.

It was found that the manometer recorded the contraction before the patient was aware of pain. The patients complained of the pain just a few seconds before the contraction had reached its maximum and ceased to complain several seconds before relaxation was complete. It was also observed that there was no definite uniformity in intensity of successive contractions; one strong contraction might be followed by another strong contraction or even a weaker or stronger contraction. There was throughout the entire first stage a rather definite regularity in the occurrence of contractions but occasionally a second contraction set in before there was complete relaxation from the first contraction.

Almost invaribly there was a slowing of the fetal heart rate while the contraction was at its height; this slowing was followed by a temporary increase in rate during the interval between contractions.

SUMMARY AND CONCLUSIONS

1. Although the artificial apparatus described in this paper may have some inaccuracies, yet by its use much valuable information concerning uterine pressure has been obtained.

2. From the values obtained, it can be said that the intrauterine pressure bears no relationship to either the volume of the uterus or the amount of amniotic fluid.

3. In primiparas, the intrauterine pressure seems to be inversely proportional to the duration of the labor.

4. Evidently the pressure created by the accessory powers of labor is transmitted directly to the fetus through the uterine wall because of the much greater pressure values obtained during the second stage of labor.

5. From this series of cases the total average relative intrauterine pressure value was 32.1 mm. of mercury. The maximum average was 49.9 mm. of mercury. In each case the average relative intrauterine pressure was obtained by adding all the pressure values for each pain and then dividing by the number of pains. The averages were then added and the total divided by the number of cases giving the total average value.

6. The relative intrauterine pressure value in this series did not exceed 125 mm. of mercury.

7. The occurrence of several superimposed, severe contractions could produce a slowing of the fetal heart rate sufficiently to cause anoxemia of the fetus with resulting fetal asphyxia. This may explain in a measure the fetal mortality during the first stages of labor.

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1020 MEDICAL ARTS BUILDING

CYSTIC ENDOMETRIAL CHANGES IN OVULATORY CYCLES*

THE MIXED ENDOMETRIUM

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INCLUDED in our collection of over 1,000 endometrial biopsy specimens secured at various phases of normal and abnormal menstrual cycles are five that do not conform to the usual cyclical variations originally described by Hitschmann and Adler. On the contrary these specimens present a *mixed* histologic picture containing characteristics of both the proliferative (cystic) and the secretory phases at a time when only secretory characteristics should be evident. This combination does not appear to have been noted heretofore.

The endometrium during the normal menstrual cycle goes through a series of changes dependent upon a concomitant cycle of events in the ovary. The follicular hormone† dominates the first half of the cycle and stimulates the proliferation of the endometrium. During this stage the endometrium is characterized by the presence of narrow straight nonsecreting glands lined by pseudostratified epithelium and by a dense stroma composed of deeply staining spindle cells.

Following ovulation the ruptured follicle is transformed into a corpus luteum, and the latter produces a hormone called progesterone. Al-

*Read at a meeting of the Bronx Pathological Society, January 19, 1937.

†Since the various estrogenic hormones have been isolated in crystalline form, and their chemical structure identified, it becomes possible to designate them by their chemical names. The dosage may be stated in milligrams when a pure hormone preparation is used. The hormone which is secreted by the follicle is estradiol. This hormone is then excreted through the urine as estrone (or theelin, estrin, progynon) and estriol (or theelol). Amniotin and emmenin are mixtures of estrogenic compounds. It is advisable, whenever possible, to substitute milligrams or gamma (1 mg. = 1000 gamma) for the rat or mouse unit. The biologic unit varies greatly, depending upon the numerous conditions which influence the method of standardization, while a milligram of hormone remains the same quantity under all conditions. Many investigators have accepted 1 rat unit to be the equivalent of 5 gamma of crystalline estradiol benzoate. Because of the rapidity with which estradiol is excreted, it is usually coupled with benzoic acid to form an ester (the phenolic benzoate is commercially known as progynon-B). The mouse unit varies from about 0.04 gamma to 0.1 gamma of pure estrone depending upon the procedures employed in the different laboratories. The ratio between the rat and mouse units is somewhere within the limits 1:4 to 1:9.

With the advent of crystalline corpus luteum hormone, progesterone, 1 mg. of the hormone is equal to one International Unit. One Clauberg Unit is the equivalent of 0.5 mg., and one Allen Unit is the equivalent of 1 mg. of crystalline progesterone.

though the follicular hormone continues its activity during the second phase of the cycle, the corpus luteum hormone dominates the picture and converts the endometrium into the secretory stage.* The latter is characterized by the large, convoluted, saw-toothed secreting glands, lined by simple, columnar epithelium. The stroma is composed of large pale polygonal cells. Shortly before the onset of menstruation the stroma becomes markedly edematous and hemorrhagic, and the entire endometrium assumes a cloudy, "cooked" appearance. During menstruation the functional layer of endometrium is cast off and the defect is soon repaired by the regeneration of glandular and stromal elements of the basal layer.

Should ovulation fail to occur, the follicle persists and the endometrium remains in the proliferative phase. If the action of the estradiol, secreted by the persistent follicle, is prolonged and unopposed by progesterone, the endometrium assumes a swiss-cheese pattern. It becomes thick due to an increase in the number and size of the glands, many of which are enormously dilated. The histologic characteristics of the glands and stroma are the same as in the simple proliferative endometrium. Although the cystic endometrium is frequently associated with excessive bleeding, this bleeding differs from true menstruation in that it is unaccompanied by true endometrial desquamation.

We have found five specimens of mixed endometrium in biopsies on four women with disturbed menstrual cycles.† The following study of the pathogenesis of the mixed endometrium was made in order to elucidate the nature of the underlying derangement of ovarian function.

CASE REPORTS

CASE 1.—Oligomenorrhea, mixed endometrium. M. R., aged 34, para ii, onset of menses at 14 years, periods regular every four weeks, moderate flow of six to seven days without dysmenorrhea. Following a regular six-day period (Aug. 16 to 21, 1934) there was amenorrhea for two months. This was succeeded by irregular, occasionally profuse bleeding for three months which ended on Jan. 18, 1935. Two months later profuse bleeding recurred and continued for two weeks (Mar. 14 to 28, 1935) when the patient entered the hospital.

Examination at this time revealed a uterus of normal size and an absence of adnexal pathology. An endometrial specimen on April 1, 1935 showed marked cystic hyperplasia (Fig. 1, *A*) but the smaller glands were in an early secretory stage (Fig. 1, *B*). The stroma cells had proliferative characteristics. The patient flowed moderately from April 4 to 10, 1935. This could have been a menstrual period. On April 30, 1935 another biopsy was taken and again revealed a similar mixed picture. A menstrual flow followed from May 2 to 7, 1935.

The first specimen revealed a mixed endometrium following a prolonged cycle. The same appearance was noted in the second specimen after a cycle of normal length.

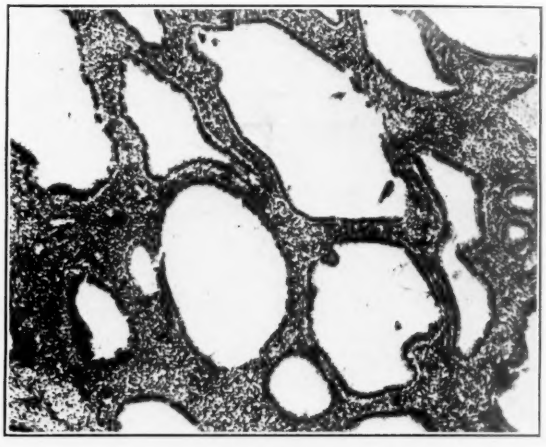
CASE 2.—Oligomenorrhea, mixed endometrium. D. P., aged 31, onset of menses at 16 years, periods occurred at intervals of two to three months, moderate flow for ten days without dysmenorrhea. Following her only pregnancy in 1929, the periods

*This secretory transformation proceeds in an irregular patchy fashion so that for a short time following ovulation the same endometrial specimen may reveal some areas in the proliferative phase and others in the secretory phase. Traut and Kuder[1] have recently referred to this temporary *transitional* endometrium as "irregular ripening." We have excluded it, however, from our concept of a mixed endometrium.

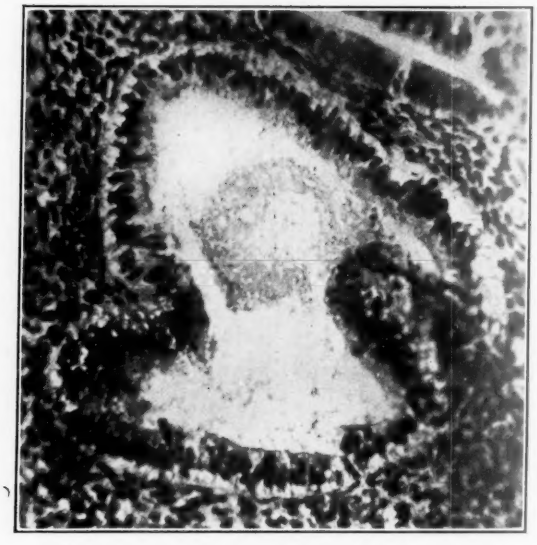
†Since this paper was submitted for publication, we have obtained twelve additional specimens.

came regularly every twenty-eight days, but the flow was now of one to two days' duration and scanty in amount. In 1934 the prolonged cycle returned but the short scanty flow persisted.

The last regular period was Feb. 12 to 13, 1935. Beginning April 13, 1935, she stained until April 27, 1935, when a biopsy was taken. This revealed a typical cystic endometrium. One week later (May 4, 1935) biopsy again showed a cystic



A.



B.

Fig. 1.—Case 1. (*A*) Mixed endometrium. Amenorrhea for two months followed by two weeks' bleeding. Cystic endometrium contains some secreting glands. (*B*) Actively secreting gland (high power).

endometrium (Fig. 2) but the stroma cells were now pale and large and closely resembled those of the secretory phase. A secretory epithelium was not present, however. The patient had what she described as a "regular period" on May 12 to 14, 1935.

The following three periods occurred at twenty-seven-day intervals, the last period being Aug. 27 and 28, 1935. The periods from September through November

were skipped. A biopsy on Nov. 16, 1935 showed an early proliferative endometrium with small nonsecreting glands and a dense stroma. Another biopsy three weeks later (Dec. 7, 1935) revealed a typical secretory endometrium. A five-day flow began on the following day. Thus, the last delayed cycle showed no mixed features. The delay though limited to the follicular phase was unaccompanied by cystic changes.

CASE 3.—Oligomenorrhea, mixed endometrium. H. C., aged 23 years, onset of menses at 15, regular every twenty-eight days, moderate five-day flow without dysmenorrhea. Last regular period Dec. 10 to 14, 1935. The next period was skipped and on Feb. 17, 1936 she began to flow moderately. The bleeding however continued until March 28, 1936 when a curettage was performed. The uterus was normal in size and consistency; both ovaries were slightly enlarged. The curettings revealed large cystic glands lined by pseudostratified epithelium and, finally, small glands lined by simple cuboidal epithelium. The latter glands gave the impression of having recently been secreting but actual secretion was not seen. The stroma cells

Fig. 2.—Case 2. Mixed endometrium. Endometrium cystic but stroma cells are large and pale resembling those of a secretory endometrium.

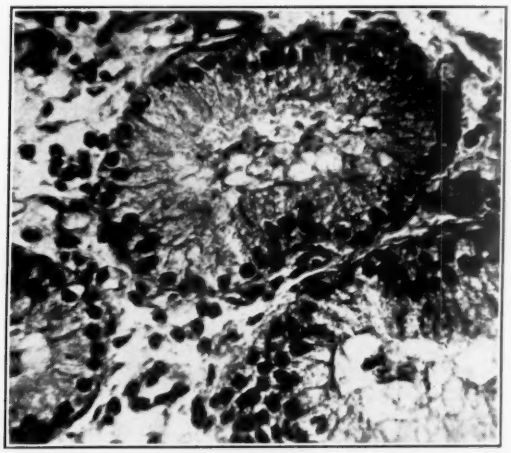
were large and pale, and there were many areas of pericapillary edema. The stroma was as of the secretory phase; most of the glands resembled those of the cystic endometrium. There was no evidence of gestation.

The next period occurred on Apr. 15 to 19, 1936. On May 9, 1936 prior to the expected date of the subsequent menstruation, biopsy revealed a typical secretory endometrium.

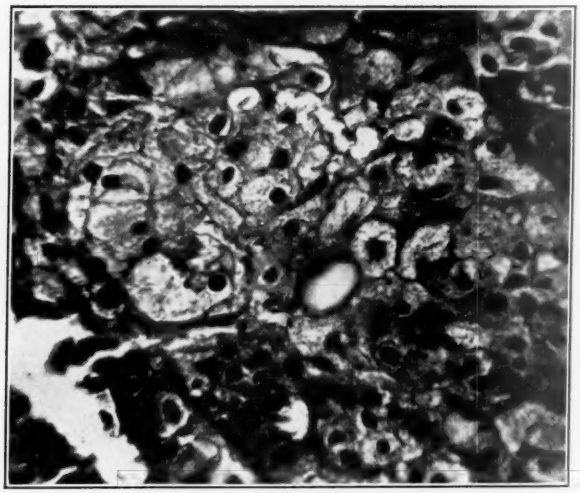
Thus in a young woman with a previously normal menstrual cycle, a delayed period was followed by prolonged bleeding and the endometrium showed a mixed picture. The normal menstrual rhythm then returned.

CASE 4.—Secondary amenorrhea, mixed endometrium. S. M., aged 35, amenorrhea of two years' duration. Menses irregular since onset at 14 years. No genital hypoplasia. Basal metabolism was minus 4 per cent. Normal urinary hormone findings, no follicle-stimulating hormone; 10 to 40 R.U. of follicular hormone per liter. Biopsy specimens obtained at intervals during a period of one and a half years showed the proliferative phase at times and the secretory picture at other times.

A.



B.



C.

Fig. 3.—Case 4. Secondary amenorrhea with ovulatory cycle. Mixed endometrium. (*A*) Cystic glands, secreting glands, edematous stroma. (*B*) Actively secreting glands (high power). (*C*) Decidual-like stroma cells (high power).

The administration of large doses of progynon-B was followed by regular scanty periods. On several of these occasions biopsy showed a secretory endometrium. The periods stopped after discontinuation of treatment on July 18, 1935. An endometrial biopsy (Fig. 3, *A*) on Oct. 1, 1935 revealed many round dilated glands lined by simple cuboidal epithelium and, in addition, normal-size actively secreting glands lined by simple columnar epithelium (Fig. 3, *B*). The stroma was markedly edematous and contained large pale decidual-like cells with well-defined outlines (Fig. 3, *C*).

This woman was thus ovulating without menstruating. On the occasion that a mixed endometrium was found, there was probably some antecedent derangement of the ovarian cycle which was reflected in the endometrium.

DISCUSSION

There are four possible ways in which a mixed endometrium might develop:

1. *Excessive production of follicular hormone during the follicular portion of the cycle.* This would result in the formation of a cystic endometrium to which secretory effects would be added following ovulation.

2. *Excessive production of follicular hormone during the luteal phase.* This probably does not occur in nature, but we tried to simulate such a condition by administering 40,000 R.U. of progynon-B (200 mg.) during the last two weeks of a normal menstrual cycle. The period occurred a few days earlier than usual. The secretory endometrium obtained by biopsy at the onset of the flow while extraordinarily thick showed no cystic changes. Perhaps there was insufficient time for cystic glands to develop or perhaps they are unable to develop once the endometrium has been influenced by the corpus luteum.

3. *Excessive production of progesterone during the follicular stage.* This appears impossible in nature because the corpus luteum does not form until the proliferative phase is complete. If progesterone were injected during the early part of the follicular phase, it would probably find the endometrium unable to respond. In the characteristic cystic endometrium, which is merely an overgrown proliferative endometrium, ovulation and luteinization characteristically fail to occur. However, when progesterone is administered in these cases, the endometrium is cast off before mixed features can develop.

4. *Excessive production of progesterone during the luteal phase.* It is questionable if this occurs at all. If it did, it would probably merely intensify the secretory effects already present.

Our experience with late menstrual (ovulatory) cycles indicates that the delay is due entirely to prolongation of the follicular phase. This is in agreement with the opinion of Campbell[2] that the duration of the luteal phase is limited to about fourteen days. The persistence of an actively secreting corpus luteum beyond this period must be a rarity. We have never encountered an endometrial section that suggested this condition. Possibly the premenstrual administration of progesterone

would prolong the secretory phase. The spontaneous occurrence of a mixed endometrium is therefore limited to ovulatory cycles in which the estrogenic hormone exerts an excessive influence during the follicular portion of the cycle. To the cystic endometrium thus produced secretory characteristics are added following ovulation.

In three of the four cases described above, the interval between periods was prolonged. This intermenstrual delay seems to be significant because of the additional time permitted the follicular hormone to exert an undue influence on the endometrium. However, a mixed endometrium may also occur in cycles of normal length. The only essential condition is that sufficient estrogenic hormone is secreted prior to ovulation to make the endometrium cystic. We have been able to produce a cystic endometrium experimentally within two weeks by administering 80,000 R.U. of progynon-B (40 mg.) during the first half of the cycle. Prolongation of the follicular phase does not necessarily result in a mixed endometrium because the hormone production in many cases of oligomenorrhea is definitely subnormal.

We next attempted to produce this mixed histologic picture experimentally. The two following methods seemed reasonable:

1. The administration of large doses of *estrogenic hormone* during the follicular portion of a normal ovulatory cycle.

2. The administration of large doses of *progesterone* during an anovulatory cycle associated with a "swiss-cheese" endometrium.

CASE 5.—*Estrogenic hormone, delayed period, mixed endometrium.* M. C., aged 27, marked lower girdle adiposity, para iv. Menses regular since onset at 13, twenty-eight day cycle, three or four days, moderate flow, without dysmenorrhea. Genital tract normal.

The patient had a regular period from Oct. 28 to 31, 1935. Two injections of progynon-B (10,000 R.U. each) were given on Nov. 2 and 9, 1935. The following period was two weeks late (Dec. 9 to 12, 1935). Biopsy on Nov. 23, 1935 revealed a proliferative endometrium. One week later (Nov. 30, 1935) the endometrium was in the early secretory phase, and the following week (Dec. 7, 1935) in a late secretory phase. The last biopsy revealed an area of large cystic glands lined by simple columnar epithelium. The stroma cells were large and there was considerable edema of the stroma. By delaying the period only the follicular phase was prolonged. This permitted the formation of cystic areas in the endometrium which, following ovulation, underwent secretory transformation.

A similar experiment was performed on the same patient using a larger amount of estrogenic hormone. The last regular period was Oct. 15 to 18, 1936. Progynon-B (20,000 R.U.) was injected on Oct. 20, 1936 and again on Oct. 27, 1936. The following period was also delayed two weeks (Nov. 27 to 30, 1936). Biopsy on Nov. 10, 1936 showed a proliferative endometrium (Fig. 4), on Nov. 17, 1936 an early secretory endometrium but, in addition, several areas with markedly dilated glands (Fig. 5). The cystic glands were lined by a nonsecreting pseudostratified epithelium while the stroma was typical of the secretory phase. On Nov. 24, 1936 a third biopsy revealed a late secretory endometrium (Fig. 6). The stroma was markedly edematous and hemorrhagic. A few glands were slightly dilated. Here again was a delayed period with a prolonged proliferative phase and cystic glands. Finally ovulation occurred and the secretory transformation proceeded at the usual

pace. When 80,000 R.U. of progynon-B were given to this patient during the first half of the cycle, a cystic endometrium was found two weeks after the onset of the period. Subsequent weekly biopsies revealed the return to an ordinary proliferative endometrium when the injections were discontinued. Ovulation occurred during the fifth week and menstruation during the seventh week.

We then attempted to produce the mixed endometrium in another way, by the administration of large doses of progesterone to two women with persistent cystic endometrial hyperplasia.

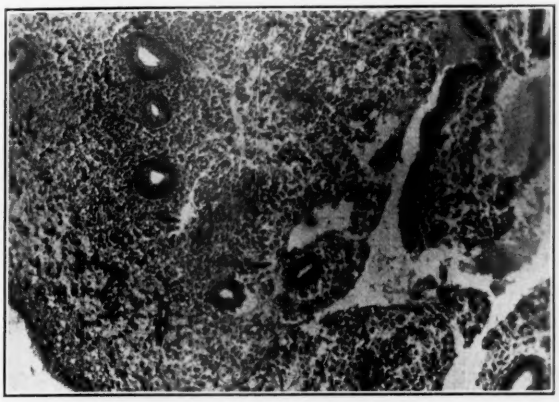


Fig. 4.—Case 5. Experimental production of mixed endometrium. Early proliferative phase four weeks after last period. Next period delayed two weeks by 40,000 R. U. progynon-B.

Fig. 5.—Case 5. One week later. Mixed endometrium. Small glands adjoining the cystic glands in early secretory stage.

CASE 6.—*Maturity bleeding, cystic endometrium, progesterone.* M. P., aged 34, married twelve years, never pregnant. Onset of menses at 14 years. Periods regular the first six months only; then became totally irregular alternating between amenorrhea and profuse and prolonged bleeding. For the past ten years the bleeding has been almost constant though not always profuse. Patient has marked obesity of the trunk type. Numerous biopsies during the past four years have consistently revealed a "swiss-cheese" endometrium. Intensive therapy with pregnancy urine extract (follutein-Squibb) converted the almost continuous bleeding into a more moderate periodic flow but without appreciable change in the endometrium.

The last flow was Sept. 24 to Oct. 3, 1935. Biopsy at the onset of the flow showed a cystic endometrium. Five rabbit unit doses of progesterone (proluton-Schering) were injected on Oct. 22, 24, 26, and 29, 1935. A profuse flow followed on Oct. 28, 1935 and continued to Nov. 3, 1935. Biopsy on Nov. 2, 1935 revealed a postmenstrual type of proliferative endometrium with small straight, nonsecreting glands lined by pseudostratified epithelium. The stroma cells, however, were much larger than would be expected to accompany the glands; they were pale and resembled

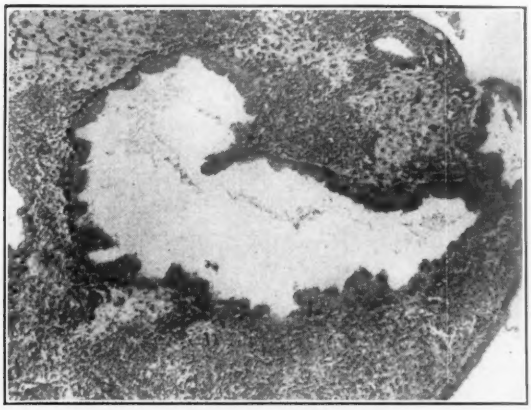


Fig. 6.—Case 5. The following week. Late secretory endometrium.

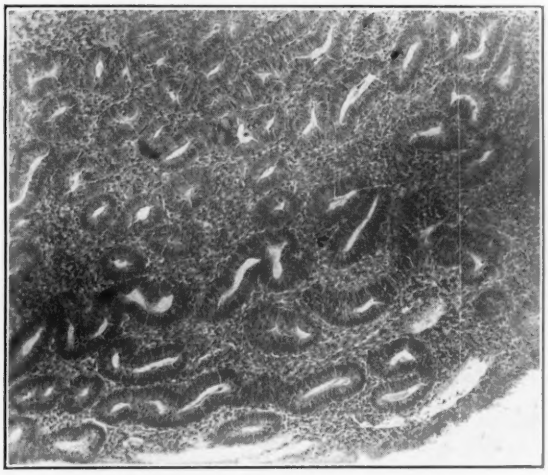


Fig. 7.—Case 6. Endometrium after 45 Rb. U. of progesterone. Small glands in proliferative phase. No cystic glands present.

more the stroma cells of the premenstrual endometrium. Subsequently, after progesterone was discontinued, the cystic endometrium reappeared.

Another attempt was made six weeks later using a total of 45 rabbit units of progesterone (5 Rb. U. every other day). After the fourth injection bleeding occurred and, again, biopsy revealed a postmenstrual proliferative endometrium. The cystic endometrium under the influence of the corpus luteum hormone was apparently cast off and replaced by a new endometrium (Fig. 7). The small new glands did not show secretion probably because they had not developed sufficiently. Clauberg[3] and Hamblen[4] previously reported similar observations. The endometrium

subsequently became cystic again. The temporary shedding of endometrium induced by progesterone is thus equivalent to a curettage. Browne[5] has also made the same observations.

CASE 7.—*Puberty bleeding, cystic endometrium, progesterone.* J. L., aged 20, onset of menses at 15 years, cycle always irregular, profuse flow of four to ten days' duration at intervals of two to six weeks. Patient bled profusely and continuously from Dec. 5, 1932 to Jan. 10, 1933. The hemoglobin was 40 per cent. Curettings revealed a "swiss-cheese" endometrium. After intensive therapy with pregnancy urine extract the bleeding stopped. Five blood transfusions were necessary to combat the anemia. Following this episode, there was no bleeding for eight months. Another period of bleeding then ensued but was quickly controlled with the same form of therapy. Subsequently there was complete amenorrhea for twenty-seven months, during which time biopsies revealed a persistence of the cystic endometrium.

Progesterone in 5 Rb. U. doses was administered every third day for five doses beginning Mar. 23, 1936. Following the second injection staining occurred and continued for one week. Biopsy on Apr. 10, 1936 revealed a proliferative endometrium. A few slightly dilated glands were seen but none were cystic. The stroma cells were small.

On May 19, 1936 the same experiment was repeated. This was followed by bleeding. Biopsy again showed endometrial glands of the usual type but the stroma cells were considerably larger than would be expected at this stage of a normal menstrual cycle. Thus the stroma alone showed the progesterone influence.

SUMMARY AND CONCLUSIONS

1. A mixed endometrium is described. It is characterized by the presence of cystic glands in association with secreting glands, or decidual-like stroma cells, or both.

2. The pathogenesis of the mixed endometrium is discussed. Its spontaneous occurrence is limited to ovulatory cycles in which there is excessive action of the estrogenic hormone during the follicular phase. The latter may or may not be delayed.

3. The mixed endometrium was experimentally produced in a woman with normal menses by prolonging and intensifying the follicular phase by means of estrogenic hormone. The attempt to produce it by the administration of progesterone during anovulatory cycles was unsuccessful due to endometrial desquamation.

4. The significance of the mixed endometrium is as follows: it demonstrates that the endometrium is an accurate indicator of the different phases of ovarian function.

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FULL-TERM ABDOMINAL PREGNANCY WITH RECOVERY OF BOTH MOTHER AND BABY

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THE following is a history of a full-term abdominal pregnancy, operated upon on Sept. 14, 1936, by the senior author (W. D. C.).

Patient M. G., white, American, 29 years of age, was admitted to the Columbus Hospital on Sept. 14, 1936, with a diagnosis of a transverse presentation, and possible dystocia due to a fibroid. Her last period was Dec. 6, 1935. Her previous history was negative except that four years ago she had a tuboovarian infection which confined her to bed for six weeks. Repeated smears at that time were negative for Neisserian infection. Two years ago a mastectomy for a Schimmelbusch disease of the left breast was done (W. D. C.).

When the patient was first seen in February, 1936, the uterus was only slightly enlarged and the patient complained of hyperemesis gravidarum. Glucose and corpus luteum intravenously cleared up her vomiting. An Aschheim-Zondek test done by Dr. Casilli was positive. Her red cell count was 3,300,000; Wassermann and Kahn tests, negative; urine, negative; hemoglobin, 50 per cent. The patient improved and had no other symptoms.

At seven months her abdomen became abnormally distended. It was transversely ovoid and at that time she was informed that she had a malpresentation. Blood pressure and urine were negative. Her initial weight was 115 pounds and on admission to the hospital it was 137½ pounds.

At full term, x-ray confirmed the diagnosis of transverse presentation. Fetal parts were easily palpable. The head was in the left iliac fossa and the extremities in the right iliac fossa and the convexity of the back toward the pelvic inlet. A mass could be palpated below and to the left of the umbilicus which on palpation would harden and then disappear. Fetal heart was plainly audible to the left and below the umbilicus (140 beats per minute).

We saw the patient in consultation on Sept. 14, 1936, and agreed that a transverse presentation in a primipara with normal pelvic measurements and a normal sized child was unusual, and that she might have a fibroid obstructing the inlet. However, we were not satisfied that this mass was a fibroid because it had a tendency to soften, and we believed it might be a part of the uterus. Rectal examination revealed a firm cervix with no dilatation of the external os and a marked fluctuation in the cul-de-sac of Douglas. No fetal parts could be palpated by rectum. Being a primipara with a transverse presentation, with a rigid cervix and a possibility of a mass, cesarean section was advised.

We attempted external version with no result. A low cervical cesarean section was planned, but on opening the abdomen, the uterus was found about the size of a three months' pregnancy. It was injected, flattened anteroposteriorly, and arising from its posterior surface and both sides was a tremendous sac with large tortuous vessels. Passing the hand upwards, it was possible to feel the placenta. An abdominal pregnancy was diagnosed. The omentum covered the sac like an umbrella, with large vessels leading from the omentum into the placenta. On each side, the amniotic sac was fused with the colon. Above the uterus was an area about three inches in diameter which appeared free of vascularity and through which an incision was made. The child was then easily delivered and it started to breathe at once. Bleeding by this time was profuse so immediately the sac cavity was packed. The question then arose as to how the placenta should be handled; to leave it in

and sew up the abdomen, to marsupialize it, or to remove it. It was possible to get a hand under the omentum close to the transverse colon and stomach. It was clamped and cut between clamps and on reaching the splenic flexure of the transverse colon, a line of cleavage was found, and the amniotic sac peeled quite readily from the descending colon and pelvic colon. But on the right side, part of the placenta and amniotic sac was firmly adherent to the appendix which was removed. The abdomen was sewed up tight. While being bandaged she passed from her vagina a piece of membranous tissue which proved to be true uterine cast composed of decidual cells without villi.

The patient was in shock, pulse was 160 for three days. She received three transfusions 700 c.c., 300 c.c., and 300 c.c. Continuous venoclysis of 5 per cent glucose in normal saline was given. At 5 A.M. on the second day, she developed an acute dilatation of the stomach, and with the use of a Levine tube, supplemented by the use of eserine, she rallied. Temperature remained at 103° F., and pulse at 160 for three days. On the fourth day, both temperature and pulse came down to normal. She was up on the thirteenth day after delivery and home on the seventeenth day. The child was a normal child weighing 5 pounds 14 ounces, at birth, and 6 pounds 9 ounces on discharge from the hospital.

In retrospect, the salient features in this case were: (1) Previous history of tuboovarian infection. (2) Failure of the uterus to enlarge commensurate with the date of pregnancy. (3) Sudden distention of the abdomen after seven months. (4) The abnormal presentation. (5) The presence of a mass in the lower abdomen which felt like a fibroid. (6) The boggy fluctuation of the cul-de-sac.

Traina, G.: The Uterus in Hydatidiform Moles, Monatschr. f. Geburtsh. u. Gynäk. **104**: 82, 1936.

In cases of hydatid moles there are two dangers. The first lies in the mole itself and consists of hemorrhage, toxic symptoms, destruction of the uterus, embolism, infection, etc. The second danger is the possibility of a malignant change resulting in a chorionepithelioma. Among the studied 11 patients with moles, 6 were between forty-one and forty-nine years of age. This is in accordance with the view that hydatid moles occur chiefly during the preclimacteric period. A very small mole may be expelled completely. Large ones have a tendency to penetrate veins and the uterine wall.

As a result of his histologic study of the 11 uteri, the author believes the following are suspicious but not definite indications of malignancy: large masses of growing epithelial elements, either in the decidua or the uterine muscle, and the duration of the viability of these cells even when there are not many present. If the body cannot destroy these cells in due time, they may lead to a chorionepithelioma. A curettement does not necessarily imply complete removal of a hydatid mole. The only certain way to determine the absence or presence of living molar tissue is by means of the Aschheim-Zondek test.

All women who have had hydatid moles should be carefully followed up. In some cases the bleeding which follows is due not to the development of a malignant condition but to degeneration and infection of retained molar products. A positive Aschheim-Zondek test indicates live chorionic tissue.

In most cases where ovarian cysts are present in cases of hydatid mole, the cysts disappear after the mole is removed. Should these cysts remain, the uterus should be investigated for tissue which was not removed.

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Editorial Comment

The Trend of Modern Obstetrics

THAT progress should be measured by favorable results, applies to medicine or specifically to obstetrics as it does to other activities. Recent years have witnessed remarkable changes and improvements in the conduct of pregnancy and labor. Dissatisfied with the record of fatalities attending childbearing, the profession has undertaken the task of developing corrective measures, adequately aided by other groups which have associated themselves in the task of providing adequate and satisfactory obstetric care. Public interest has stimulated the institution of numerous agencies which have discussed means and methods of making childbearing safe. The causes of the high maternal death rate of this country have been sought and evaluated.

A noteworthy contribution is that made by Dr. Frank W. Lynch at the last Clinical Congress of the American College of Surgeons in which a frank discussion was presented dealing with the relation of "radical" obstetrics to maternal mortality. As pointed out by Lynch and other competent observers, improved methods of anesthesia and operative technique and the increased opportunities for interference with labor afforded by hospitalization of obstetric patients, have developed radical tendencies entirely out of step with the ultraconservative views of former days. As Lynch so well states "the radical school feels that childbirth in the hands of nature is too crude to fit in with the ideas of modern life." Much surgery has followed but whether for good remains to be seen. Moreover we are confronted with the fact that it has had little effect in reducing maternal mortality, therefore we must question the merit of its aims notwithstanding the claims made by the defenders of radical methods, that morbidity and mortality are thus reduced. Improved public health and other facilities in developing better hygiene of pregnancy have cut down the incidence of toxemia and similar states; but shock, hemorrhage and sepsis maintain their toll of victims, and these must be ascribed to other factors.

Judgment respecting fatalities has taken on new meanings since the preventability factor was featured in the New York Academy of Medicine Report on Maternal Mortality. Lynch considers that in some centers the maternal mortality rate actually has risen because the deaths termed "preventable are increasing faster than the nonpreventable deaths are decreasing."

Claims have been made that it is unfair to judge the matter in this fashion, because many of these deaths occurred in the hands of untrained men and the responsibility therefore cannot be ascribed to those with a radical point of view but who, as a matter of fact, are more expert. This evades the question, for we can only judge the final outcome by good average care in a country so widespread and as large as the United States. Radicalism in obstetric practice cannot be said to have compensated the outlay in means and effort which have been expanded, if we are to judge by the final results. What should be done to institute a levelling process? Lynch believes that the new school of obstetrics needs proper molding by the adequate control of men and procedures and proposes that only well-qualified operators be allowed to undertake major obstetric surgery.

Maternal mortality rates may not interest the untrained obstetrician but they are of interest to governmental agencies and may serve, rightly or wrongly, as a prominent factor in the possible introduction of a certain degree at least of Federal control of medical practice. One may differ from this thought. Education, not legislation, is the proper and the better remedy and this must be self-imposed. Organized medicine is doing its share. The American College of Surgeons has instituted a supervisory service for accredited hospitals but the loop-holes exist in our numerous independent institutions, often dominated mistakenly as maternity hospitals, which do not follow accepted standards of admission to their privileges and afford opportunities to the general practitioner who thus attempts more than he is qualified to do by training or equipment.

Fortunately, most confinements terminate normally, but we have interposed routine analgesia for pain relief, we have attempted short cuts in labor, we have developed operative terminations to delivery where these are uncalled for, we have neglected or set aside the "obstetric conscience." This appears as an arraignment which undoubtedly will be resented, but the facts based on prevalent high maternal, stillbirth, and neonatal mortality rates, call for a revision of present-day practices if we are to show any improvement.

Medical schools cannot train all of their students as expert obstetricians. They are equipped to furnish merely the ground work. Graduate education in obstetrics undoubtedly is improving, but there are not sufficient opportunities for acquiring the judgment and technical skill which is so essential for the proper conduct of labor. If, as Lynch believes, we must develop more competently staffed maternity services in general hospitals, so that a larger group can obtain adequate experience, that suggestion should be given earnest consideration. However, this will be of little avail unless we can come to some fairly definite agreement about the limitations concerned with conservatism and radicalism in obstetric procedures. In view of the prevailing differences of opinion this will not be a simple task but, like many other problems of medical practice, it can best be solved by the profession itself and constitutes a challenge which must be met. American obstetrics has reached a high estate; it can well undertake to solve its problems.

Epidemic Diarrhea of the Newborn

FOR several years reports have been published of outbreaks of diarrhea in the newborn with a resultant case mortality rate reaching as high as 45 per cent. The disease is epidemic in character but has many mysterious features: post-mortem examinations and various laboratory tests have failed to reveal any definite information of its etiology or transmission. Various observers claim that this disease constitutes a well-defined clinical entity and deserves consideration apart from other diarrheal disturbances of infancy. Epidemics have been reported in several of our larger American cities and likewise in Europe. Within a three-year period New York had 27 outbreaks in 19 different hospitals. Chicago has had similar experiences. The problem is a serious one and until we know more about it, methods of attack necessarily must reside in preventive measures directed to the probable entrance of infection, namely the baby's nose and mouth, which means that institutional obstetric and nursing technique be developed with this end in view.

The epidemic evidently is limited to institutions and with the constantly mounting number of hospital confinements, especially in our larger cities, control measures must include not only the handling of an individual outbreak by accepted methods employed in communicable diseases, but the prevention of further outbreaks by a thorough study of the physical equipment of the particular delivery service. The obstetrician's responsibility in this problem is a very evident one. Maternity hospitals, some in name only, have expanded greatly and largely without adequate control of either staff or facilities. Nurseries in many of these are conducted on the principle of "mass collective care" without regard in certain instances to the most elementary principles of sanitation and asepsis. It is essential that health departments and other supervisory agencies develop adequate means and methods of inspection and control over lying-in hospitals and nursing homes, so that the loss of lives among the newborn from this source be checked. If the profession and the public demand hospital care for delivery, the element of danger to life must be avoided for the baby as well as the mother. Both are at a premium.

Dr. John L. Rice, Health Commissioner of New York City, has emphasized the need for sensitizing the country against this epidemic, so that more satisfactory information may be developed for combating it. If due to overcrowded nurseries or to breaks in their aseptic conduct, the measures of prevention should not be far to seek.

The responsibility for instituting reform resides, however, in the obstetrician as much as in the pediatrist, although to the latter there is delegated in many instances, the care of the newborn. If more definite cooperation is needed to obtain the desired improvement, further cooperative efforts must be developed to overcome this unfortunate epidemic disease, with its resultant high mortality rate.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A SURVEY OF 447 MATERNAL DEATHS OCCURRING IN THE COUNTIES OF MARYLAND DURING THE YEARS 1930-1936 (INCLUSIVE)

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DURING recent years the high maternal mortality rates throughout the United States have received increasing attention from physicians, health authorities, and lay press, alike. A number of statistical analyses dealing with this subject have appeared, most of them recounting the record of maternity hospitals or the experience of large cities. In 1933 the Children's Bureau of the Department of Labor published an exhaustive report on "Maternal Mortality in Fifteen States" for the years 1927 and 1928. Comprehensive analyses of results in smaller communities and rural areas have been few. Knox, in 1931, wrote a brief analysis of 241 maternal deaths occurring in the counties of Maryland, exclusive of the city of Baltimore, during the years 1927 to 1929, inclusive. This survey was made possible by data accumulated through personal interviews with the physician or midwife concerned in each instance. Since the above date, the practice of making surveys on all maternal deaths has continued and over the seven-year period ending Dec. 31, 1936, an additional 447 cases have been recorded. The following comprises an analysis of the various items of information obtained from the survey blanks as transmitted to the State Department of Health.

It should be emphasized in advance that these 447 maternal deaths occurred in the counties and do not include a number of rural patients transported to and dying in the hospitals of Baltimore. Maryland, exclusive of Baltimore, is predominantly rural, and there are only four other cities in the state with a population in excess of 10,000. The topography of the state varies from low-lying areas bordering on the Chesapeake Bay, to rich farm lands, to mountainous mining districts. The occupation of the inhabitants varies accordingly and the racial distribution is such that in one county the number of colored births is in excess of the white, while in another not a single one of the former is recorded. In other words, it is felt that the childbearing population of the state affords a representative cross section of the country and that conclusions drawn from this study may be applied to other sections.

Race.—Investigators throughout the United States have generally reported a higher maternal mortality rate in colored than in white women. Over an eleven-year period ending in 1935, the average death rate from puerperal causes in the counties of Maryland was 4.06 per 1,000 live births (white) as contrasted with 6.84 (black).

TABLE I. BIRTH AND MATERNAL DEATH STATISTICS, ACCORDING TO RACE

	LIVE BIRTHS COUNTIES MARYLAND, 1934	DEATHS ABORTION	DEATHS OTHER	TOTAL DEATHS
White	10,951	80	241	321
Black	2,913	14	112	126
White	78.99%	85.11%	68.27%	71.81%
Black	21.01	14.89	31.73	28.19

The same racial disparity is illustrated in Table I. Deaths listed as abortion do not include ectopic pregnancy, therapeutic abortion, or undelivered women dying prior to the seventh month of pregnancy. The contrast between these deaths and those occurring in late pregnancy, labor, and the puerperium is significant as is evidenced by the following ratios (approximate) found for the colored race: total births 1 in 5; deaths abortion, 1 in 7; deaths other, 1 in 3. It is believed that the column "deaths other" reveals the true racial difference more accurately than does "total deaths" since the majority of abortion deaths were due to sepsis following criminal procedures, and it is uncommon for the colored woman to employ active means towards the premature termination of a pregnancy.

TABLE IIA. AGE OF WOMEN IN SERIES AT TIME OF DEATH SUBDIVIDED BY RACE AND PARITY (OMITTING UNKNOWN)

AGE	WHITE				BLACK				TOTAL WHITE		TOTAL BLACK	
	PRIMIPARAS		MULTIPARAS		PRIMIPARAS		MULTIPARAS					
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
-14	4	3.74	0	0.00	3	6.25	0	0.00	4	1.25	3	2.38
15-19	41	38.32	8	5.13	28	58.33	5	8.62	50	15.58	35	27.78
20-24	30	28.04	15	9.62	11	22.92	10	17.24	58	18.07	24	19.05
25-29	15	14.02	24	15.38	1	2.08	10	17.24	57	17.76	18	14.29
30-34	10	9.35	25	16.03	2	4.17	11	18.97	48	14.95	18	14.29
35-39	3	2.80	50	32.05	2	4.17	11	18.97	59	18.38	15	11.90
40-44	4	3.74	32	20.51	1	2.08	7	12.07	43	13.40	9	7.14
45-	0	0.00	2	1.28	0	0.00	4	6.90	2	0.62	4	3.17
Total	107	100.01	156	100.00	48	100.00	58	100.01	321	100.01	126	100.01

TABLE IIB. MEAN AGE OF WOMEN ACCORDING TO BIRTHS (U. S., 1934) AND DEATHS (MARYLAND, 1930-1936)

	BIRTHS		MATERNAL DEATHS	
	YEARS	MONTHS	YEARS	MONTHS
White, primiparas	23	3	23	0
multiparas	29	6	33	10
Black, primiparas	20	4	20	6
multiparas	27	11	31	10
Total, white	27	6	29	7
black	25	10	27	0

Age.—It is generally stated that early childbearing is to be preferred from an obstetric standpoint and statistical analyses have appeared indicating that the course of pregnancy, labor, and the puerperium in the "young primipara" (aged 16 or less) is accompanied by a minimum of complications and a favorable maternal and fetal mortality. Conversely, elderly primiparity (aged 35 or more) is usually believed to be attended by increasing hazards to mother and child, although little has been said concerning the effect of advancing age upon the multiparous woman.

Tables II A and II B and Figs. 1 to 3 indicate the frequency distribution of the women in this series according to age at the time of death, with subdivisions for race and parity. Furthermore, a contrast is offered between this item and the age of moth-

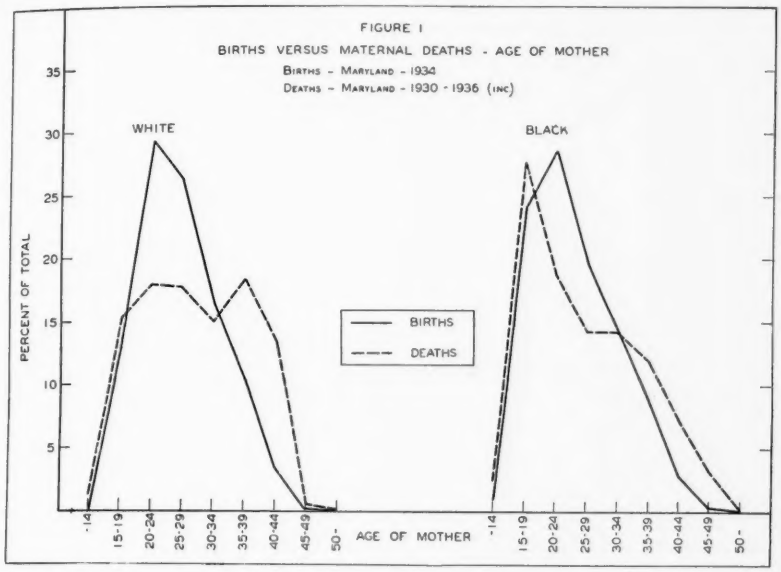

Fig. 1.

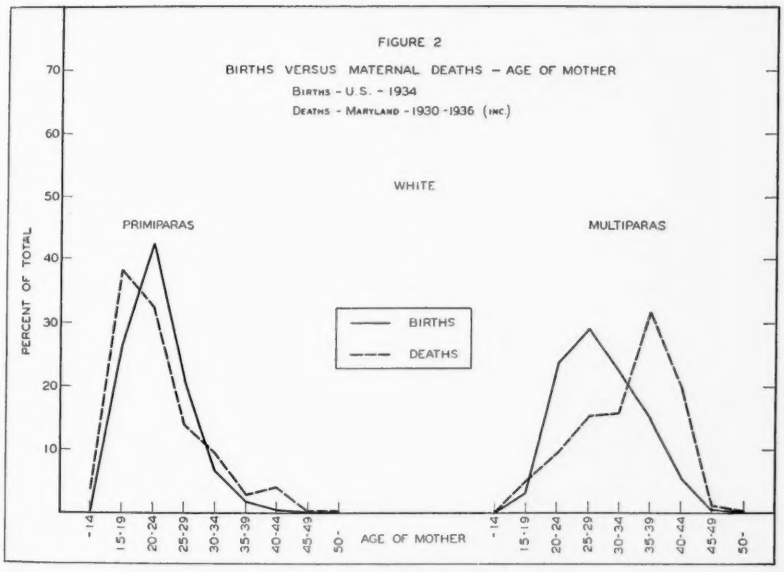

Fig. 2.

ers at the time of primiparous or multiparous births for the United States Registration Area in 1934, since a comparison between the percentage of total births versus deaths for any age group should afford an indication of the risk involved. Our experience indicates that childbirth occurring before the age of twenty is accompanied

by an increased hazard to the mother as is evidenced by these comparative percentages of total births and maternal deaths: white primiparas 27.03 and 42.06; white multiparas 3.34 and 5.13; black primiparas 56.66 and 64.68; and black multiparas

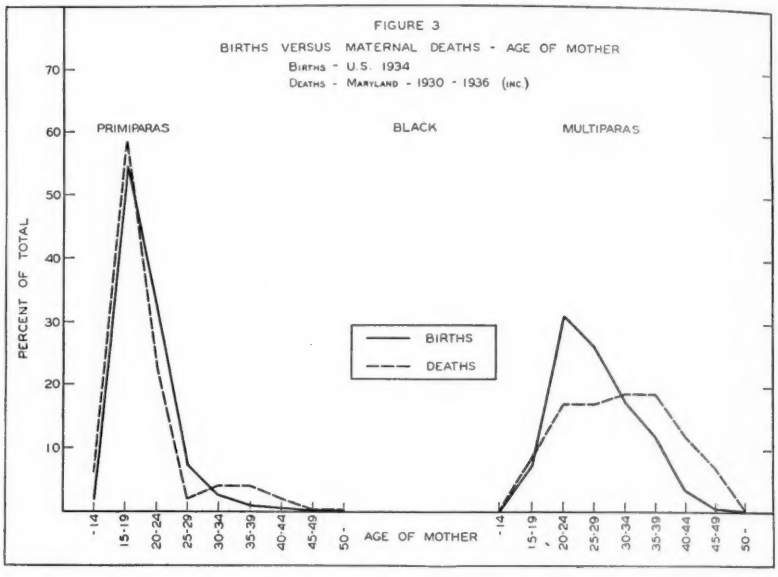

Fig. 3.

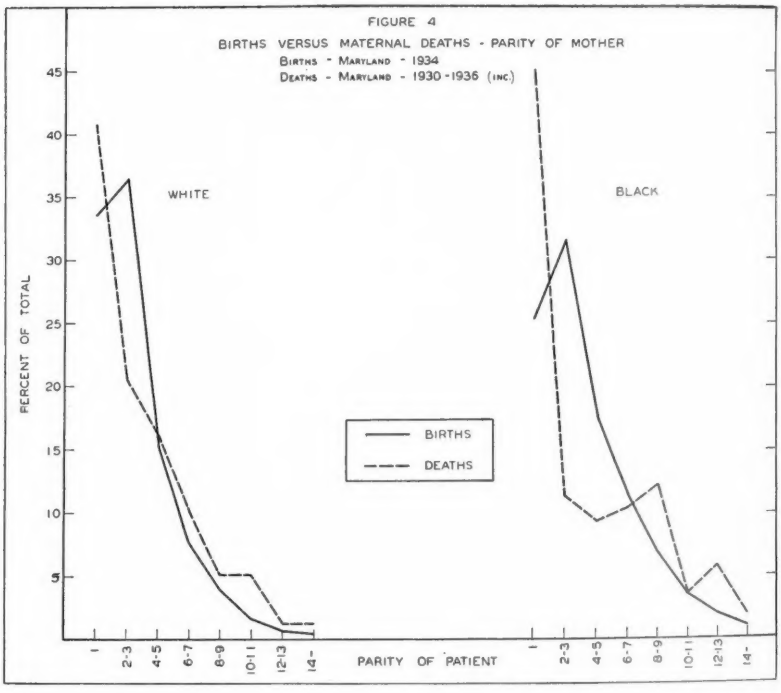

Fig. 4.

8.12 and 8.62, respectively. Calculated on a similar basis, the age group 20 to 34 inclusive may be considered the safest, our figures indicating a low percentage of total deaths as contrasted to births. As the end of the childbearing period nears, pregnancy is again accompanied by increased danger, particularly to the multipara as is indicated by the following percentages of births and deaths, respectively: white multiparas 20.83 and 53.84; and black multiparas 16.16 and 37.94. The above findings are further emphasized by a comparison of total births and deaths according to mean age as is shown in Table IIB. The mean age at time of death of the white multiparas in the series was four years and four months in excess of the figure derived for average age at time of delivery; while for colored multiparas a similar increase of three years eleven months was found. In other words, our experience indicates that the practice of dismissing the multiparas, aged thirty-five or more, with the term "normal" is a dangerous one, and it is in this group of women that a great many of the avoidable maternal deaths occur.

Parity.—The distribution according to parity of the women in the series is shown in Table III, while Fig. 4 affords the same contrast between total deaths and births as has been used in the discussion of effect of age. This figure indicates the expected increased hazards of primiparity, which are disproportionately high in the black as contrasted with the white woman. In the white race the second and third baby seem by far the safest to the mother and when the group para iv and v is reached, the percentage of total deaths exceeds that of births, and this discrepancy continues throughout the higher multiparous brackets, so that the incidence of total births,

TABLE III. DISTRIBUTION OF MATERNAL DEATHS ACCORDING TO PARITY (OMITTING UNKNOWN)

PARITY	NUMBER		PER CENT	
	WHITE	BLACK	WHITE	BLACK
i	107	48	40.68	45.28
ii-iii	54	12	20.54	11.32
iv-v	42	10	15.97	9.43
vi-vii	26	11	9.88	10.38
viii-ix	14	13	5.32	12.26
x-xi	14	4	5.32	3.77
xii-xiii	3	6	1.14	5.66
xiv	3	2	1.14	1.89
Total	263	106	99.99	99.99

para iv and over, is 29.97, while the comparative figure for total deaths is 38.77 per cent. In colored women the incidence of deaths does not exceed that of births until the bracket para viii and over is reached and the contrasting figures here are 23.58 and 13.83 per cent, respectively. The reasons for this observed racial difference are not clear and may well be a sampling error alone. We believe, however, that these figures serve to emphasize once more the fact that the "grande multipara" is not a satisfactory obstetric subject, runs an increased chance of such major complications as placenta previa, rupture of the uterus, premature separation, transverse presentation, etc., and should be cared for accordingly.

TABLE IV. DISTRIBUTION OF MATERNAL DEATHS ACCORDING TO SOCIAL STATUS

	NUMBER						PER CENT					
	ABORTIONS		TOTAL WITHOUT ABORTIONS		TOTAL		TOTAL WITHOUT ABORTIONS		ABORTIONS		TOTAL	
	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK
Married	60	10	222	74	282	84	75.00	71.43	92.12	66.07	87.85	66.67
Single	19	3	16	37	35	40	23.75	21.43	6.64	33.04	10.90	31.75
Widowed	0	1	2	1	2	2	0.00	7.14	0.83	0.89	0.62	1.59
Divorced	1	0	1	0	2	0	1.25	0.00	0.41	0.00	0.62	0.00
Total	80	14	241	112	321	126						

Social Status.—The social status of the 447 women in the series is shown in Table IV. The high incidence, 25 per cent white and 28.57 per cent black, of illegitimate pregnancies in patients dying after abortion was to be expected. Excluding abortions, and due probably to inadequate obstetric care, the percentage of unmarried mothers in the series of maternal deaths was 6.64 and 33.14 for whites and blacks, respectively. A comparison is offered by the recording as illegitimate of 2.63 per cent of total births white and 23.81 per cent black in 1934 for the State of Maryland.

Prenatal Care.—It is axiomatic that adequate maternity care must include not only skilled attention at the time of delivery but also careful supervision throughout the entire pregnancy. Our figures indicate that two-thirds of women dying of puerperal causes in the counties of Maryland had never sought medical aid prior to the onset of labor or the fatal illness and that only one out of ten had had adequate prenatal care. Some difficulty was experienced in assaying the adequacy or inadequacy of prenatal supervision from the information available. It was arbitrarily determined to classify as "good" the prenatal care of those patients who had sought advice before the seventh month of pregnancy, had been seen at least twice before labor by the physician, and whose examination had included a general physical check-up, pelvic mensuration, blood pressure determination, and urinalysis. The blood Wassermann test was not included because it had been done so rarely. In a number of instances the woman was examined relatively early in pregnancy but was not seen again until delivery; the care in such cases was classified as "inadequate." Table V gives the data available on prenatal care and omits all pregnancies terminating within the first four months. It will be noted that antepartum supervision was received much more frequently by the white than the colored women in the series and that this supervision was adequate in 15.49 per cent of the former group as compared with 0.93 per cent of the latter. Furthermore, a total of 76 white and 12 colored women sought medical advice at or before the seventh month of pregnancy yet good care was experienced by only 35 of the former and one of the latter group. Table V also shows that of those women seeking prenatal care almost all had the urine examined for albumin and in the vast majority of instances the blood pressure was determined. However, in only slightly more than half, 55.56 per cent, was any attempt at pelvic mensuration made and usually this examination did not include the determination of the diagonal conjugate nor was the intertuberous diameter estimated. Finally, the Wassermann reaction was obtained only 20 times, 6.01 per cent of the patients in the series. These figures clearly indicate that two of the major weapons of modern obstetrics, namely the diagnosis of pre-existing abnormalities and the early recognition of obstetric complications, were rarely employed in this series of 447 maternal deaths. It should be emphasized that this statement must not be considered as criticism of the attendant physician for re-

TABLE V. PRENATAL CARE OF WOMEN IN SERIES (OMITTING ABORTIONS)

	NUMBER		PER CENT OF TOTAL		PER CENT TOTAL	PER CENT OF PRENATAL PTS.	
	WHITE	BLACK	WHITE	BLACK		WHITE	BLACK
Good	35	1	15.49	0.93	10.81		
Inadequate	57	17	25.22	15.89	22.22		
None or unknown	134	89	59.29	83.18	66.97		
Month First Seen							
-5	55	3	24.34	2.80	17.42	59.78	16.67
6-7	21	9	9.29	8.41	9.01	22.83	50.00
8-	12	6	5.31	5.61	5.41	13.04	33.33
Unknown	4	0	1.77	0.00	1.20	4.35	0.00
Pelvis measured	47	13	20.80	12.15	18.02	51.09	72.22
Urine examined	91	16	40.27	14.95	32.13	98.91	88.89
Blood pressure determined	85	16	37.61	14.95	30.33	92.39	88.89
Wassermann done	14	6	6.19	5.61	6.01	15.22	33.33

peatedly the statement appears on the survey "was not called to see this patient until shortly before her death." It is impossible to state how many of these deaths might have been avoided had the woman sought advice during the antenatal period, but an analysis of the records leads one to believe that adequate supervision at this time might have altered the end result in a substantial number of instances.

Place of Delivery.—Table VI indicates the place of delivery, or of death in those cases dying undelivered, of the cases under analysis, abortion deaths being omitted. Home and hospital deliveries seem to be about equal, but it is our belief that the information if complete would indicate a preponderance in favor of the home since in a number of cases home delivery was planned and admission to the hospital sought later because of the diagnosis of some obstetric complication.

TABLE VI. PLACE OF DELIVERY, OR DEATH, IF DIED UNDELIVERED (OMITTING ABORTIONS AND UNKNOWN)

	NO.	PER CENT
Home	156	46.29
Undelivered, died at home	16	4.75
Hospital	139	41.25
Undelivered, died in hospital	25	7.42
Undelivered, died on way to hospital	1	0.30
Total	337	

Place of Death.—Information as to place of death is given in Table VII which indicates that approximately one-third of the total deaths occurred at home although 45 women who had been delivered of viable children were transferred to hospitals at some time, usually late, in the course of the fatal illness.

TABLE VII. PLACE OF DEATH

	NO.	PER CENT	
Delivered home, died hospital	45	10.07	
Delivered hospital, died hospital	136	30.43	
Died undelivered, hospital	25	5.59	65.33
Abortion, died hospital	83	18.57	
Delivery unknown, died hospital	3	0.67	
Delivered hospital, died home	3	0.67	
Delivered home, died home	111	24.83	
Died undelivered, home	16	3.58	34.45
Abortion, died home	24	5.37	
Undelivered, died on way to hospital	1	0.22	

Duration of Pregnancy.—Analysis of the case records from the standpoint of duration of pregnancy revealed two points worthy of mention. A fourth of the total deaths followed abortion or occurred before delivery during the previable stage of the pregnancy. It will be shown subsequently that in the great majority of these cases the cause of death was postabortal sepsis, usually following criminal procedures. This is considered a large figure and attains added importance since, under

TABLE VIII. DURATION OF PREGNANCY AT TIME OF DELIVERY OR DEATH

	NO.	PER CENT	PER CENT WITHOUT UNKNOWN
Term	214	47.87	52.07
Premature	83	18.57	20.19
Abortion	114	25.50	27.74
Unknown, not abortion	36	8.05	

existing social conditions, the prevention of such deaths seems impossible. In only slightly more than half of the total cases, 52.07 per cent, had the pregnancy reached term.

Type of Delivery.—Table IX indicates the outcome to the pregnancy in the deaths under consideration. Eleven women died as the result of ruptured ectopic pregnancy, the diagnosis being confirmed at operation in 6 instances. Two deaths followed therapeutic abortion, the indication for the operative termination of pregnancy being myomata uteri and chronic nephritis, with death resulting from surgical shock following hysterectomy, and post-partum hemorrhage after curettage, respectively. Other postabortal deaths totaled 94. Almost 10 per cent of the deaths occurred before delivery, 7 being in the previable stage of pregnancy. The type of delivery (viable) was unknown in 19 instances. There remain 279 women delivered of viable fetuses, 205 of which had reached approximate maturity. Birth was spontaneous in only a little more than half of these, 57.71 per cent, with operative procedures as detailed in Table IX being employed in the remainder. Delivery by version was noted more frequently than forceps, the indication for this operation in the majority of instances being placenta previa or eclampsia. Attention is directed to the fact that 49 women died following delivery by cesarean section, 17.56 per cent of total viable births. The indication for the operation could not be ascertained from the survey blanks in 22 instances but *in 22 of the remaining 27 it was eclampsia!* The causes of death in the 49 section cases were eclampsia 21, puerperal sepsis 11, intestinal obstruction 3, and operative shock 2, with the operation itself apparently not a causative factor in the other 12.

TABLE IX. TYPE OF DELIVERY WITH REFERENCE TO DURATION OF PREGNANCY

Ectopic pregnancy		11		
Laparotomy	6			
Died without operation	5			
Therapeutic abortion		2		
Hysterectomy	1			
Dilatation and curettage	1			
Other abortions		94		
Died undelivered		42		
Type of delivery unknown		19		
Delivery at or near term		279		
	NO.	PER CENT	TERM ONLY NO.	TERM ONLY PER CENT
Spontaneous	161	57.71	123	60.00
Forceps	27	9.68	17	8.29
Version	32	11.47	18	8.78
Breech extraction	8	2.87	6	2.93
Craniotomy	2	0.72	2	0.98
Cesarean section	49	17.56	39	19.02

Attendant at Time of Delivery.—Table X shows that for viable births delivery was effected by a physician in 9 cases out of 10. In a number of instances, however, care by a midwife was planned and the doctor summoned only because of some obstetric complication.

TABLE X. ATTENDANT AT TIME OF DELIVERY (VIABLE BIRTHS ONLY)

	NO.	PER CENT
Delivered by:		
Doctor	267	89.60
Midwife	21	7.05
Neighbor	1	0.34
No attendant	6	2.01
Unknown	3	1.01

Outcome to Child.—From Table XI it will be seen that, including abortions in order to ascertain the result of total pregnancies, only 43 per cent of the cases under consideration terminated in the birth of a living child. Considering only viable births a stillborn rate of approximately 1 out of 3 was obtained.

TABLE XI. OUTCOME TO CHILD

	NO.	PER CENT	PER CENT
Abortion	107	23.16	
Undelivered	42	9.09	
Stillborn	109	23.59	34.28
Alive	199	43.07	65.72
Unknown	5	1.08	

Cause of Death.—The discussion as to cause of death of the patients in the series will be given under the following two headings: (1) The cause as given on the death certificate and classified according to the international list of causes of death. This is done in order to contrast the results found with those of the United States Registration Area both total and rural. (2) A more complete listing of individual causes than is usually made in statistical analyses from maternity hospitals.

Making use of the International Classification and contrasting our experience with that for the country as a whole, several interesting points become apparent, as illustrated in Table XII. Abortion without sepsis occurs about equally in the white

TABLE XII. CAUSE OF DEATH ACCORDING TO INTERNATIONAL CLASSIFICATION INCLUDING A COMPARISON WITH THE UNITED STATES REGISTRATION AREA

(Omitting 9 White and 5 Colored Women Dying of Pneumonia)

	MARYLAND			U.S.	U.S.
	W.	C.	TOTAL	U.S.	RURAL
Abortion with sepsis	67	10	77	2037	480
Abortion without sepsis	6	2	8	640	272
Ectopic with sepsis	1	0	1	121	20
Ectopic without sepsis	6	3	9	489	93
Other accidents of pregnancy	1	0	1	88	32
Placenta previa	20	5	25	411	141
Other hemorrhage	24	7	31	928	371
Puerperal sepsis	40	30	70	2719	901
Puerperal tetanus	0	0	0	10	2
Albuminuria and eclampsia	89	47	136	2520	1110
Other toxemias	5	1	6	535	131
Phlegmasia, embolus, sudden death	27	4	31	592	234
Other accidents of childbirth	25	11	36	1750	650
Other conditions of puerperal state	1	1	2	45	11
	312	121	433	12885	4448

	MARYLAND			U.S.	U.S.
	W. %	C. %	TOTAL %	U.S. %	RURAL %
Abortion with sepsis	21.47	8.26	17.78	15.81	10.79
Abortion without sepsis	1.92	1.65	1.85	4.97	6.12
Ectopic with sepsis	0.32	0.00	0.23	0.94	0.45
Ectopic without sepsis	1.92	2.48	2.08	3.80	2.09
Other accidents of pregnancy	0.32	0.00	0.23	0.68	0.72
Placenta previa	6.41	4.13	5.77	3.19	3.17
Other hemorrhage	7.69	5.79	7.16	7.20	8.34
Puerperal sepsis	12.82	24.79	16.17	21.10	20.26
Puerperal tetanus	0.00	0.00	0.00	0.08	0.04
Albuminuria and eclampsia	28.53	38.84	31.41	19.56	24.96
Other toxemias	1.60	0.83	1.39	4.15	2.95
Phlegmasia, embolus, sudden death	8.65	3.31	7.16	4.59	5.26
Other accidents of childbirth	8.01	9.09	8.31	13.58	14.61
Other conditions of puerperal state	0.32	0.83	0.46	0.35	0.25

and black women and has a much lower incidence in Maryland than for the country as a whole. However, abortion with sepsis results fatally almost two and a half times as often in white as contrasted with colored patients, and the incidence here is definitely higher than for the total registration area. It is believed that the great majority of deaths listed under this latter heading are the results of criminal procedures. If this be accepted, the racial discrepancy is easily explained, since it is rare for the pregnant negress to employ active measures to terminate gestation. However, the finding of a higher incidence of abortion deaths in this, a series of rural women, as contrasted with the entire country is a disturbing and serious matter. Deaths following ectopic pregnancy occurred about equally in the two races and the incidence was about that for the registration area. Of the total colored deaths, 9.92 per cent were ascribed to placenta previa and other hemorrhage, while for white women the higher rate of 14.10 per cent was found. The only suggestive cause for this difference was the much greater number of operative procedures employed to effect delivery in the white women, whereas most of the colored were allowed to deliver spontaneously. Hemorrhage deaths occurred somewhat more frequently in this series than for the entire country. Puerperal sepsis (omitting postabortal infection) was listed twice as often in the colored as in the white column, despite a higher operative incidence for the latter group. This affords

TABLE XIII. APPARENT CAUSE OF DEATH FROM INFORMATION ON SURVEY BLANKS AND DISREGARDING DEATH CERTIFICATE

		%
I. Infection:		143 = 31.99
Puerperal sepsis	64	
Postabortal sepsis	77	
Intrapartum septicemia	1	
Septicemia, operation, ruptured ectopic	1	
II. Toxemia:		123 = 27.52
Eclampsia	94	
Chronic nephritis	25	
Toxemic vomiting	3	
Acute yellow atrophy	1	
III. Hemorrhage:		74 = 16.55
Post-partum hemorrhage	21	
Premature separation of placenta	8	
Placenta previa	25	
Ruptured ectopic	9	
Ruptured uterus	3	
Hemorrhage with abortion	7	
Inversion of uterus	1	
IV. Other Obstetric Complications:		53 = 11.86
Embolus	26	
Shock, delivery	18	
Intestinal obstruction after C.S.	3	
Anesthetic death	2	
Acute poisoning, attempt at abortion	2	
Pernicious anemia of pregnancy	1	
Paralytic ileus, post partum	1	
V. Nonobstetric Complications:		32 = 7.16
Chronic valvular heart disease	8	
Pneumonia	15	
Influenza	2	
Pyelitis	2	
Acute mania	2	
Status epilepticus	1	
Perinephritic abscess	1	
Peritonitis, cause unknown, undelivered	1	
VI. Unknown		22 = 4.92

further evidence of an interesting and not understood racial difference repeatedly found by investigators. The total incidence of sepsis for the series is well under that for the Registration Area. Attention is called to the finding of a higher rate of postabortal sepsis than of infection following delivery of a viable child. The toxemias of pregnancy accounted for 30.13 per cent of the white deaths and 49.67 per cent of the black. It is believed that the racial difference is probably in terms of prenatal care which, as has been seen, was utilized more frequently by the white patient. The incidence of toxemic deaths was significantly higher in this series than in the entire country. To recapitulate, deaths from sepsis and toxemia occurred more frequently in the black than in the white women of the series, whereas the reverse was found for postabortal sepsis and hemorrhage. Also, in comparison with the United States Registration Area (rural) the counties of Maryland showed a favorable balance in deaths from puerperal sepsis but an unfavorable one for abortion and toxemia.

Analyzing the survey blanks carefully and listing individually the causes of death, it was found that infection, toxemia, and hemorrhage, in order of frequency as listed, accounted for 76.06 per cent of the total. It has been frequently stated that in the United States 40 per cent of all maternal deaths are due to infection. The figure of 31.99 per cent adduced here compares favorably with this. Toxemia follows closely upon infection as a cause of death with eclampsia accounting for the greatest number under this category. It seems likely that the figure of 94 fatalities ascribed to eclampsia is too low, and we believe that more careful diagnosis would have resulted in some of the 25 listed as chronic nephritis being placed in the former category. Those cases listed under hemorrhage seem to call for no particular comment at this time. In 22 instances information obtained from survey was too incomplete to permit an independent diagnosis being made.

DISCUSSION

A statistical analysis has been presented of 447 maternal deaths occurring in the counties of Maryland, exclusive of Baltimore City, during the years 1930 to 1936, inclusive. Comment upon the findings has been made with the summary of each individual item. Further discussion may well be limited to two points: A comparison of the experience here listed with that obtaining elsewhere; and an attempt to evaluate means of avoiding those which in the light of present medical knowledge must be listed as "preventable."

The maternal death rate for the entire state of Maryland in 1934 (the last year in which complete comparative figures were available at the time of writing), was 5.2 per 1,000 live births, and for the counties 4.2, while for the United States Registration Area, it was 5.9. Only 11 states reported a lower figure and in 3 others an identical one was found. The results in Maryland become even more favorable when it is noted that those states reporting a lower mortality rate have a much smaller colored population, and as has been stated, puerperal deaths in white women in Maryland counties over a period of eleven years was only 4.06 per 1,000 live births. It is obvious, however, that even this figure is far too high and by no means represents an approach to a minimum of what might be termed "unavoidable deaths."

The information obtained from survey was in many instances too meager to furnish a definite statement as to whether or not the death might be considered avoidable, or the responsibility placed on the patient, physician, or midwife. In many cases it seemed that the patient herself was definitely responsible, either because of failure to obtain suitable medical care or through lack of cooperation with her doctor.

In other instances the physician or midwife could have been implicated by an error in judgment or technique. In this regard certain statistics found in a report on "Maternal Mortality in New York City" published in 1933 are of interest. Following an exhaustive survey of 2,041 maternal deaths it was concluded that 1,343 or 65.8 per cent must be classed as preventable and that the responsibility lay with the physician in 61.1 per cent of the latter, the patient in 36.7 per cent, and the midwife in 2.2 per cent. To what extent the experience of urban New York may be comparable to rural Maryland is difficult to estimate. It is, however, our opinion that approximately two-thirds of the 447 maternal deaths which we have analyzed were strictly preventable, that in many instances the patient herself was responsible through failure to seek and obtain prenatal care, while frequently the community was to blame because of the absence of local facilities for such care. No adequate solution to this problem has ever been presented but it is believed that adequate dissemination of contraceptive material and advice throughout the rural communities might accomplish something. However, it must be admitted that in many instances contraception, in view of present methods and the low intelligence standard of those most needing such advice, would at best serve only to delay the inevitable pregnancy. Deaths from abortion without sepsis were in the main due to bleeding. Fatal hemorrhage with abortion is not ordinarily fulminant but a protracted process enduring over a period of days. In several of our cases it seems evident that had medical advice been sought before the patient was almost exsanguinated the fatal outcome might have been avoided. Since in many rural areas prompt medical attention is not always available and hospitalization often entails many miles of transportation, deaths from *ectopic gestation* are rarely avoidable. *Placenta previa* and *other hemorrhage* accounted for approximately one-eighth of the total deaths in this series. In New York City it was stated that 76.1 per cent of such deaths were preventable and that in four-fifths of these the physician or midwife was at fault. This high degree of preventability undoubtedly exists in urban areas but in isolated communities without adequately equipped hospitals the majority are probably unavoidable. The counties of Maryland compare favorably with the rural United States in deaths due to *puerperal sepsis*. Here the untrained and slovenly midwife is often at fault, although it must be admitted that many births occur in huts so primitive and filthy as to render clean obstetrics impossible. It is believed that unsatisfactory home conditions afford as urgent an indication for hospital delivery as do the major obstetric complications. However, beds for the "normal multipara" are usually not available and in many communities can be had only by the paying patient. Current tendencies toward operative obstetrics undoubtedly account for many sepsis deaths but this is true far oftener in urban than in rural communities. Almost a third of the deaths here reported were due to *albuminuria, eclampsia,* and *other toxemias,* and it is in this group that the greatest number of preventable deaths occur, with the patient herself usually at fault. Adequate prenatal care would probably have prevented the toxemia from becoming severe enough to endanger life in three cases out of four. Even in New York City it was felt that the responsibility lay with the patient in 69.0 per cent of the toxemic deaths. Deaths from *phlegmasia, embolus,* and *sudden death* are rarely avoidable in view of present medical knowledge.

It must be said, however, that *other accidents of childbirth* are largely preventable and must ascribed to errors of technique or judgment on the part of physician or midwife. Major operative procedures are too frequently attempted without proper indication, in an unfavorable environment, and on patients unable to withstand surgical trauma. Generally speaking the best results will coincide with the fewest operative deliveries.

In view of what has been said it is believed that the following recommendations offer a practical method for the reduction of rural maternal mortality.

1. The advantages of prenatal care should be made known to every pregnant woman and adequate care should be immediately available to her. Despite an earnest attempt on the part of the medical profession and considerable recent publicity by the lay press the average rural woman does not seek examination and advice in the antenatal period unless symptoms develop which are sufficiently disquieting to persuade her to do so. The relatively rare so-called "full pay" patient is an exception to this and in most rural areas of our experience seems to be seeking and obtaining relatively adequate prenatal supervision. The majority of white women of a lower financial scale call the physician only after labor supervenes. The remainder of this group and most of the colored women plan to be delivered by midwives who themselves are unable to offer intelligent advice. A slowly but steadily increasing percentage of pregnant women in the counties of Maryland have been obtaining prenatal care in recent years as the result of efforts on the part of three separate groups listed here in the order of importance.

A. The county health nurse has obtained information concerning prospective mothers of the type who need care most and has persuaded them of the benefits to be expected from it.

B. Midwives, closely supervised by local health department units, have persuaded their future patients to seek such care and in some instances have refused to deliver women who have not been examined and pronounced normal by a competent agency.

C. Patients themselves, whose childbearing has been rendered safer and more comfortable by antenatal instruction, have "sold" their ideas to their friends.

To what extent is prenatal care available to women in isolated and rural districts? The answer to this important question in so far as Maryland is concerned has recently become "Almost completely." As has been said, the paying patient may obtain it from her local physician. The indigent woman may be cared for in prenatal clinics being held regularly under the sponsorship of the Bureau of Child Hygiene, the State Health Department in one or more communities of almost every county in the state. These clinics are held with the approval of the local medical societies, from whose membership the clinic physician is often selected. Many patients are sent to the clinic by their physician, who receives routine reports of the examination. An added function of these clinics is the arranging for hospitalization of the abnormal patient. The major problem at present is that of transportation. In cases to be delivered by a midwife, and upon request by a physician where his patients are concerned, the routine clinic examinations are supplemented by home visits on the part of public health nurses who give advice, seek abnormal symptoms, and assist the patient in pre-

paring her home for delivery. It is our belief that a prenatal program of this kind, available to everyone, will materially contribute in lowering the present high maternal mortality.

2. In rural communities, and particularly in those having a large colored population, adequately trained nurse-midwives constitute at least a temporary solution to the problem of proper care during labor and the early puerperium. In two of the counties of Maryland such nurses have been supplied by the Health Department. Their duties are various. In the first place they may give instruction to the local midwives, improving their methods and technique and attending deliveries in an effort to better standards. In physicians' cases they are with the patient (who would otherwise be unattended) during labor; they detect and report any abnormality, call the physician at the appropriate time and render him skilled aid during delivery itself. If delivery occurs before the physician's arrival, the nurses are competent to attend in the emergency. They are also of value in aiding the puerperal woman and in instructing her in the care of her newborn infant. Such a program not only contributes to the care of the indigent parturient but also is of benefit to the physician since much less of his time is required for the maternity case. The nurse-midwife becomes even more important when it is realized that in some rural sections physicians are not available or if so, decline to take obstetric cases. The midwife becomes the only solution to the maternity problem, and the role of trained nurse-midwife still more important.

3. Adequate hospital beds should be provided for the indigent obstetric patient who presents any abnormality or whose home is such that decent technique becomes impossible. Certain counties have no hospitals, others do not care for nonpaying patients, and distances are often such that transportation to the public wards of a city hospital is inadvisable. Furthermore, it would seem that local funds are as properly applicable to defray hospital expenses of eclampsia or placenta previa as of typhoid fever or pneumonia.

4. "Refresher" lectures and round table discussions of the modern approach to clinical obstetric problems would seem as important to the rural practitioner as to the one residing in a university city. Such discussions should be held at meetings of the county groups under the auspices of the state medical society.

Winter, E. W.: What Is the Mechanism of Breast Secretion? Wien. Klin. Wchnschr. **49:** 654, 1936.

In experimental animals (rabbit, rat, and guinea pig) the breast secretion is due to a complex network of various substances. It is linked up with the ovarian and corpus luteum hormones which give rise to a lactation hormone probably through the anterior pituitary gland which in turn stimulates the breast glands and lactation follows. In the human being, the mechanism appears to be as follows: The cause of the onset of breast secretory function is due to a change in the concentration between ovarian and anterior pituitary hormones with the probable intermediation of the vegetative nervous system so that the anterior pituitary outweighs the ovarian secretion. In certain cases of tumors of the pituitary with definite anatomic changes associated with definite cell groups, breast secretory function has been observed. These observations seem to place the ultimate cause on a definite type of cell.

W. B. SERBIN.

Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

NINTH ANNUAL MEETING, DALLAS, TEXAS.
OCTOBER 14 to 16, 1937

The following papers were presented:

Complete Rupture of the Uterus. Drs. G. W. Gustafson and W. E. Crump (by invitation).

A Comparison of Artificial Fever Therapy and Sulfanilamide Therapy in the Treatment of Gonorrheal Infections in Women. Drs. L. M. Randall, F. H. Krusen (by invitation) and E. G. Bannick (by invitation). (For original articles, see page 230.)

Further Observations on the Role of Streptococcus in So-Called Trichomonas Vaginalis Vaginitis. Drs. G. F. Hibbert and F. C. Falls. (For original article, see page 219).

Management of Placenta Previa. Dr. David Findley. (For original article, see page 267.)

A Study of the Water, Sodium, and Energy Exchange During the Latter Part of Pregnancy. Drs. R. H. Freyberg (by invitation), R. D. Reekie (by invitation), and C. Folsome. (For original article, see page 200.)

An Analysis of a Human Ovotestis. Drs. James R. Reinberger and C. S. Simkins (by invitation). (For original article, see page 275.)

The Effect of Quinine Upon Auditory Nerve. Dr. Ray A. West. (For original article, see page 241.)

Upper Abdominal Manifestations of Pelvic Disease. Drs. Joseph L. Baer and S. A. Portis (by invitation).

Report of the Committee on Clinical Affairs. Dr. Herbert F. Vanorden.

Personal and Environmental Factors in Obstetrical and Gynecological Practice. Dr. C. M. Campbell.

One-Stage Operation for Resection of the Rectosigmoid and Rectum for Carcinoma (With or Without Hysterectomy). Dr. Jean P. Pratt. (For original article, see page 209.)

The Experimental Production of Ovulation in the Human Subject. Drs. M. Edward Davis and Arthur K. Koff (by invitation). (For original article, see page 183.)

Sterilization of Obstetric Patients in Vanderbilt University Hospital, 1925-1937. Drs. G. C. McClellan (by invitation) and L. E. Burch. (For original article, see page 249.)

A Study of 288 Primiparas Over the Age of 35 Compared With 300 Primiparas Under the Age of 25. Drs. Charles E. Galloway and Tom D. Paul. (For original article, see page 255.)

An Analysis of the Cesarean Sections Performed at the University Hospital of St. Louis. Dr. William C. Stude.

Indications and Contraindications for Cesarean Section. Dr. J. E. Kanatser.

Pelvic Measurements of 4,144 Iowa Women. Dr. William F. Mengert. (For original article, see page 260.)

Artificial Fever Therapy in Pelvic Inflammatory Disease. Drs. M. A. Darling, J. M. Berris, and M. Newman. (For original article, see page 238.)

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

Collective Review

THE PATHOLOGY OF THE OVARIAN HORMONE

With Special Reference to Its Role in Tumor Development

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FOR many years various lesions in the female reproductive tract have been attributed by some gynecologists and pathologists to disturbances in the ovarian function. The relationship, however, remained largely theoretical until recently when two new developments made possible more definite methods of investigating it. One was the attainment of potent preparations of the estrogenic substances, which are now available for attempts at the artificial production of pathologic processes in animals. The other was the elaboration of methods of extraction and measurement of the ovarian hormone which can be applied to the study of its effects on human tissues and body fluids.

The pathologic effects produced in animals by the administration of estrogenic substances include particularly the proliferation of the glandular tissues of the secondary organs of reproduction, a metaplasia of columnar to squamous epithelium, hypertrophy of the fibromuscular walls of certain hollow viscera, changes in certain of the glands of internal secretion, and probably the development of some tumors. The human lesions which may be analogous to these are certain hyperplastic and neoplastic conditions of the female and male genital tracts and perhaps changes in certain of the endocrine glands. The study of this field is recent and is still intense, but the knowledge already at hand appears to justify the recognition of a special pathology of the estrogenic or ovarian hormone.

Particularly as the cause for various tumors of the reproductive tract has the ovarian hormone been repeatedly brought before the medical public. As a result it is widely believed that such conditions as endometrial hyperplasia, fibroids of the uterus, and even carcinoma of the breast are ''due'' to the ovarian hormone. The occasional reader in the subject is too little aware of the varying relationships which lie under this word ''due'' and of the great gaps and contradictions in the evidence as well as tendencies of investigators to allow facts which merit little more than hypotheses to lead them to more or less definite conclusions.

To be able to evaluate current theories, it is necessary to understand a little about the methods of investigation, upon which the evidence to support them has been based. Two general types of approach have been employed (Table I). The first of these, the older, starts with a given condition, usually a human neoplasm for which an endocrine basis is conceivable. Then evidence is sought to demonstrate a hyperactivity of the ovary. Such evidence may take the form of a histologic investigation of the ovary itself, of a clinical study of the history and physical status of the patient, or a biologic investigation to determine the concentration of the estrogenic hormone in certain tissues or body fluids. This method is always inexact and the data collected capable of different interpretations. Yet this approach is of fundamental importance for one is dealing with the actual lesion whose cause is sought.

The second and newer method has been to begin with a known excess of estrogenic substance and to attempt by its injection, usually into laboratory animals, to produce lesions similar to those of the human being. The method is simple, accurate, and

easily controlled. To make the evidence valid for an explanation of the human lesion, however, one must make two assumptions: first, that the concentrations of hormone used in laboratory animals are comparable to conditions present in the human subject; second, that the lesion produced is morphologically identical with the human lesion which was the object of study. Both assumptions have been at times too enthusiastically and too hastily made.

TABLE I

OUTLINE OF METHODS OF INVESTIGATION OF THE RELATIONS OF THE OVARIAN HORMONE TO ABNORMAL TISSUE GROWTH

I. With the lesion present and an abnormality in hormone to be sought.

A. Human being:

1. Historical evidence of disturbances in the function of the ovary, as shown in the age of puberty and of the menopause, types of menstrual periods, and fertility.
2. Physical evidence of endocrine dysfunction, as manifested in the other glands of internal secretion, in the degree of development of the sexual organs and, in particular, in the presence of follicle cysts of the ovary and changes in the endometrium.
3. The study of the distribution of multiple tumors, which if they occur in the reproductive tract suggest a common and perhaps ovarian cause.
4. The assay of the estrogenic hormone content of the blood and urine of the patient and of the neoplastic tissue.
5. The search for an hereditary factor which if present indicates an internal, constitutional cause.
6. Observation of the effect of therapy, either the increase of ovarian stimulation by the injection of estrogenic substance or its decrease by castration.

B. Animal:

The study of the reproductive physiology of special strains of animals susceptible to spontaneous tumors is analogous to the methods outlined for the human tumors. Particularly in mice developing mammary cancer, types of estrus cycle, weights and other characteristics of the endocrine glands, the rate of excretion of estrogenic hormone, the hereditary factor and the effects of castration point the way to the studies that are necessary in man.

II. With excessive quantities of hormone available and lesions to be produced.

A. Animal.—In this field with the use of different laboratory animals, with the variation in the amount of estrogenic hormone, and with its association with other factors, the possible combinations of simple experiments become so enormous as to promise research projects for at least a generation of workers. The type of experiments which have beeen considered already may be outlined as follows:

1. The injection for a variable period of one of the several estrogenic substances.
2. The injection of one of these substances after removal of the sex gland or other organs of internal secretion.
3. The combination of an estrogenic substance with some other hormone, such as progesterone, testosterone, or anterior pituitary.
4. The combination of estrogenic hormone with some irritant, such as trauma, tar, or one of the carcinogenic tar derivatives.
5. The application of any of these principles to animals susceptible and to others resistant to tumor growth.
6. The study of the effect of estrogenic hormone on the rate of growth of spontaneous and transplantable tumors.

B. Human Being.—An attempt to produce fully developed tumors in man by injecting estrogenic hormone is, of course, impractical. Minor effects on the breast and the endometrium, perhaps pathologic, have been reported.

If evidence by one of these means is found that the estrogenic hormone is in some sense a factor in the production of a given lesion, care must be taken in correctly assessing its importance. In this respect it is useful to note several degrees of relationship.

1. The hormone may play simply a "protective" rôle maintaining the tissue in a state in which some other agent may be effective. This is the simplest explanation of why fibroids do not develop after bilateral oophorectomy.
2. The hormone may be effective only in starting the process, in causing a simple hyperplasia, while other agents are necessary to transform this to a tumor. A possible example of this is the development of carcinoma on the basis of endometrial hyperplasia.
3. The hormone may have certain indirect effects which by producing other types of stimulation lead to tumor formation. The stasis of secretions often noted in mammary ducts in which early carcinoma is present may be the result of a hormone and the cause of a chemical irritation.
4. Finally the hormone may be truly causative, but in two senses. It may represent simply a physiologic stimulus, which when effective excessively produces abnormal morphologic results, or it may be specifically tumor producing. The distinction may not be tenable, but there is probably a difference between the action of "folliculin" which when injected in the skin of the mouse's back produces only mammary tumors and that of certain of the tar derivatives which produce malignant growths in many types of tissue but particularly at the point of injection.

The application of this knowledge of the pathologic effects of estrogenic stimulation to the explanation of human lesions is a tempting field of activity. In this field theory is probably running years ahead of definite proof. In the following pages an attempt will be made to evaluate the evidence which has been brought forward for an estrogenic factor in the production of various lesions.

I. THE FEMALE PELVIC ORGANS

1. Endometrium.—For the cystic hyperplasia of the endometrium there exists of course the most complete proof of an estrogenic factor of origin. Here, as elsewhere, the ovarian function was believed to be responsible before the hormone as such had been isolated. It is useful, however, to consider experimental work first.

In the endometrium of laboratory *animals* various changes have been reported following the injection of estrogenic substances. A considerable series of experimenters claim to have produced the typical pattern of the endometrial hyperplasia found in women near the menopause (Zondek;[275] Burch, Williams and Cunningham;[30] Lacassagne;[154] Zuckerman;[281] Tietze[250]). Most workers have employed fairly large quantities of estrone, but in certain animals the amount required may be small. (Simpson and Burch.[231])

After long continued injection of these substances other effects are produced which may be analogous to certain human lesions. Metaplasia of the cylindrical into squamous epithelium has been noted by Selye and his co-workers[226] in the uterine horn of the rat and by Lacassagne[147, 154] in the mouse and rabbit.

Endometrial carcinoma has not been produced by the simple use of an estrogen. Borst[20] by combining hormone injection in rabbits with tar painting of the ears obtained a squamous metaplasia of the uterine glands, in places said to resemble cancer. Pierson[208] has reported the development in 2 of 25 rabbits injected with corpus luteum and folliculin of an infiltrating cystadenoma having all the characteristics of cancer except metastasis.

Inflammation frequently complicates the picture of estrogen effects on the endometrium, for in rats and mice the vaginal epithelium proliferates so rapidly that the uterus becomes obstructed, drainage ceases, and a pyometra follows. Long-continued experiments with large quantities of hormone are frequently a failure in these animals, owing to their premature death from infections.

Hyperplasia of the *human* endometrium was first referred to as ovarian dysfunction by Brennecke[24] in 1882, and since the work of Schröder[221] in 1915 an ovarian origin has been generally accepted. This condition remains today the most perfect example of a proved morphologic change resulting from an ovarian dysfunction in the human body, although some of the details of its mechanism are still disputed.

Schröder believed that a persistent unruptured follicle exerting its influence over an abnormally long period of time produced the hyperplastic changes. He was able to show in a number of cases the presence of hyperplasia of the endometrium, the existence of a large unruptured follicle in the ovary and an absence of any recent corpus luteum. Meyer[182] believed the condition due to a series of rapidly developing follicles, coming too close together for orderly ovulation and corpus luteum formation.

The condition of the ovaries associated with a hyperplasia of the endometrium has been studied by a long series of investigators (Babes,[8] Novak and Martzloff,[193] Beckman,[12] Shaw,[227] Graves,[106] Fluhmann[82]). Their work has tended to confirm the presence of one or more unruptured follicles and with a few exceptions the absence of fresh corpora lutea. The morphology of the endometrium too supports the view that the disease is due to an excessive or prolonged stimulation by an estrogenic hormone in the absence of any corpus luteum activity.

The attempts to demonstrate excessive estrogenic substance in the body fluids of patients with endometrial hyperplasia have not met with invariable success. Frank[85] and his co-workers noted an increase of female sex hormone in the blood and urine of patients with abnormal bleeding at puberty and before the menopause. Zondek[273] has shown the hormone to be present in excessive amounts in the fluid content of the follicular cysts and in the urine during the amenorrheic phases of polyhormonal amenorrhea associated with cystic hyperplasia. Siebke[228] found estrone in the blood especially during phases of nonbleeding.

The best examples of the dependence of hyperplasia of the endometrium upon estrogenic substance are found in the cases of granulosa cell tumor, new growths which are known to form estrogens (Schuschiana[222]) and which are always associated with endometrial changes. The production of hyperplasia in castrate women by the injection of estrogenic substances has also been accomplished (Werner and Collier[257]).

That the ovarian changes may not be the primary lesion but the disease actually dependent upon some disturbance of the anterior pituitary has been suggested by some workers (Hofbauer;[124] Burch, Williams, Wolfe and Cunningham[31]).

Some uncertainty has entered with the recognition of the occurrence of hyperplasia of the endometrium in women many years after the menopause. Reports of isolated cases of this type have been in the literature for some years (Seitz,[223] Meyer[180]), and recent articles have suggested that this may be of not infrequent occurrence. Breipohl,[23] who studied the endometria of 130 women in the menopause, noted hyperplasia in 15 or 11.53 per cent. In a recent study of patients with postmenopausal bleeding (Taylor and Millen[246]) there were found among 35 women, having no tumor or inflammatory lesion in the pelvis, 4 cases of bleeding from a hyperplastic endometrium developing four to thirteen years after the menopause. The explanation of this late hyperplasia is not clear. It may result from local causes unrelated to the ovarian function. Late follicular development may occur and perhaps be the source of estrogenic hormone. A small granulosa-cell tumor, undetected by the surgeon, is an occasional cause of late hyperplasia of the endometrium. An extraovarian source of an estrogenic substance is a final possibility.

Islands of squamous epithelium are well known to occur in the endometrium (Fluhmann[82]) and perhaps are the counterpart of the squamous metaplasia developing in laboratory animals after treatment with estrogens. Their special tendency to be associated with endometrial hyperplasia (Hintze[120]) is a little support for the view that these islands of squamous epithelium in the human uterus are estrogenic effects. That the squamous metaplasia found in some cases of endometrial carcinoma, the so-called adenoacanthoma, has a similar factor in its origin is at least a possibility.

Carcinoma of the endometrium has its peak of incidence some years after the menopause and any relation which may exist to the ovarian hormone must apparently

be a complicated one. Suggestions of an endocrine factor are found in reports of a late menopause in many of these cases (Crossen and Hobbs[62]) and perhaps in the observed association of follicle cysts of the ovary (Taylor). A somewhat promising hypothesis has been offered in the view that endometrial cancer is at times a derivative of endometrial hyperplasia and hence indirectly the result of estrogenic activity. The follow-up studies of cases of endometrial hyperplasia have, however, yielded few established examples of later carcinoma development (Hintze,[121] Mack,[175] Taylor[242]). Nevertheless the difficulty which occasionally arises in distinguishing histologically between hyperplasia and carcinoma is well known and isolated examples of carcinoma arising in areas of hyperplastic endometrium have been several times reported (Schröder,[221] Meyer,[181] Fluhmann and Stephenson[83]). Two studies (Taylor;[242] Novak and Yui[194]) of the uninvolved endometria in a series of cases of carcinoma of the corpus uteri have indicated that these glands adjacent to malignant areas are frequently hyperplastic.

2. Myometrium.—Myometrial tumors are rare in *animals,* and little experimental work has been undertaken with them. Lacassagne alone has produced what he claims to be myomatous changes in the rabbit and mouse uterus after continuous injection of folliculin. These changes did not, however, take the form of the circumscribed fibromyomas of the human uterus.

The relation of myometrial tumors to the ovary can best be demonstrated from *human* material. Frequent emphasis, beginning at least fifty years ago in an article by Hegar,[112] has been given the apparent dependence of the fibromyoma upon the ovary. Its growth is with few exceptions limited to the years of active ovarian function and atrophy usually occurs after the normal or artificial menopause. This demonstration that the ovarian hormone is necessary for the fibroid's existence is, however, no proof that it is directly causative.

Various clinical evidence has been compiled to show defects in the reproductive constitution of myoma patients. These include an alleged high incidence of sterility and dysmenorrhea and the association with other tumors (Freund,[89] Albrecht[4]).

Pathologic changes in the ovaries of patients with fibroids have, however, been the chief evidence upon which the theory of an ovarian cause has been based. This work is often dated from a paper of Seitz[223] in 1911, but Popow[209] writing in 1890 cites seven authors who had already considered the subject. The changes in the ovary reported have been extremely varied, consisting in enlargement of the whole organ, increase in the stroma and vessels, hyaline changes in vessel walls, lipoid deposits, and particularly "cystic degeneration" (Popow,[209] Bulius,[27] Mayer,[177] Moretti,[185] Albrecht[4]).

The chief protagonist of the ovarian theory in recent years has been Witherspoon.[263] He believes that "hyperestrinism," when acting over a short time, results in hyperplasia of the endometrium, when over a long time, in fibroids. He based his case on the frequent association in the same patient of cystic ovaries, myoma and endometrial hyperplasia. The evidence of Witherspoon can be attacked on two points, the strictness of his interpretation of the term hyperplasia, and the general frequency of follicle cysts. Häggstrom[108] for example in an extremely detailed study of 54 cases of fibroids found hypertrophy of the endometrium in only 4, and in his opinion cystic changes were present in the ovaries in no unusual frequency.

The finding of estrogenic hormone in considerable quantities in fibroids is of great interest (Courrier,[55] Lewis and Geschickter[164]). The significance of the observation certainly depends upon whether this high concentration is specific for tumor tissue or may be, as Frank[85] and his co-workers have suggested, not greater than that of certain normal tissues in women.

A strong stand against an ovarian dysfunction as a cause of fibroids is taken by Meyer.[180] He points out that patients with fibroids usually menstruate normally unless the position of the growth causes the bleeding, that they may become pregnant, and that no corpus luteum deficiency is demonstrable, because the endometrium often shows a pregravid mucosal pattern. Some dependence on the ovary is probable, but this may be effective through the vascular supply. Fibroids with extensive vascular adhesions to abdominal organs may continue to grow after the menopause in the presence of atrophic uterus and ovaries (Dichtl[68]).

3. Endometriosis and Adenomyosis.—The controversy over the source and route of transportation of abnormally placed endometrial tissue has overshadowed the consideration of why the ectopic endometrium should grow. The relation of the estrogenic hormone to these lesions is, however, of some theoretical importance.

a. Endometriosis of the ovary and peritoneum (Adenomyosis externa): Experimental work on endometriosis has centered chiefly on certain disputed points of the Sampson theory. It has been shown beyond question that fresh bits of rabbit endometrium implanted upon the peritoneum will grow (Jacobson[130]). Experiments indicate also that the growth of implants is less extensive in the absence of the ovaries (Brakemann,[22] Katz and Szenes[135]) and that atrophy of the implants can be prevented by injection of estrogen (Gleave[101]).

A theory postulating an ovarian factor in the origin of human endometriosis, based largely on clinical data, has also been developed. In its general implication this has been supported by numerous writers (Lauche,[162] Adler,[2] Meyer[180]). That the disease develops during the years of active ovarian function is an important fact. That atrophy occurs after the artificial menopause has been demonstrated, especially by Graves.[106] The association with other uterine new growths, particularly adenomyoma and hyperplasia of the endometrium, suggests a common origin for all (Smith,[233] Allen,[5] Jeffcoate and Potter[131]). Abnormalities of the ovaries, such as follicle cysts (Witherspoon[263]) and an absence of corpora lutea (Jeffcoate and Potter[131]) have been stressed as factors in the cause of endometriosis, as for so many other neoplastic lesions in the reproductive tract. The association of endometriosis with granulosa cell tumors has been reported (King[137]).

If, as has been maintained, carcinoma, particularly of the ovary, is sometimes a derivative of endometriosis (Sampson,[215] Reinhardt,[211] Höppner[123]), then for this malignant tumor an indirect relationship with the ovarian hormone is a possibility.

b. Adenomyosis of the uterine wall: The infiltration of the uterine musculature by endometrial tissue is another of the lesions limited to the later years of ovarian activity. An earlier inflammatory theory of origin has gradually been replaced by a vaguer conception of a decreased resistance of the myometrium against the invasion of mucosal tissue (Frankl[86]) and a pathologically increased regenerative capacity developed by the mucosa as a result of the repeated demands made upon it through menstruation (Meyer and Kitai[181]). Several writers have in general terms invoked the ovarian hormone as a factor (Meyer,[180] Albrecht,[4] Adler[2]). Pathologic changes in the ovaries (Adler,[2] Jeffcoate and Potter[131]), association with a granulosa cell tumor (Tietze[249]), and the coincidence of hyperplasia of the endometrium (Novak and Martzloff,[193] Jeffcoate and Potter[131]) have been noted as a part of the pathologic background of adenomyosis of the uterus.

4. Cervix: There appeared in 1933 a startling report by Overholser and Allen[199] who claimed to have produced a lesion resembling early cancer of the cervix in monkeys. This had been accomplished by trauma to the cervix associated with the injection of estrogenic substances. The importance of these studies depended to a large extent upon the histologic interpretation of the cervical lesions, for none of the supposed early cancers had infiltrated or metastasized. The work of Overholser and Allen has now been repeated in several species of animals (van Wagenen,[252] Zuckerman,[281] Herold and Effkemann,[116] Loeb and his co-workers,[169] Engle and Smith,[79] Hisaw and Lendrum[122]). The development of metaplasia has been confirmed, but the close relation to cancer is now denied by most workers. Overholser and Allen[200] themselves in a subsequent paper classed the process simply as a hyperplasia.

Actual cancer of the cervix has been reported in three mice treated simultaneously with theelin and 1:2::5:6 dibenzanthracene (Perry and Ginzton[204]), but here the relative importance of the two factors is difficult to determine.

Squamous metaplasia is not an uncommon finding in the *human* cervix, although usually ascribed to the irritants of chronic inflammation (Fluhmann[82]). That the ovarian hormone contributes to the change appears not improbable after a consideration of the experimentally produced lesion just described. A case of extreme epidermidalization of the cervical glands associated with a granulosa cell tumor recently came under my observation.

To associate cancer of the human cervix even remotely with the ovarian hormone will require more proof than is at present available. The disease occurs in a tissue which one is accustomed to associate less intimately with endocrine reactions than is the case with the endometrium or the breast epithelium. The coincidence of tumors of the endometrium and myometrium has been frequently reported, but cancer of the cervix appears to stand as a separate lesion.

Nevertheless an effort has been made to introduce the ovarian hormone into the background of human cervical cancer. Hofbauer[125] in particular has suggested that the well-known predilection of cervical cancer for multiparas is not due to the inflammations resulting from traumatic lesions occurring at delivery, but to the excessive hormone stimuli which the cervical epithelium is subjected to during pregnancy. As direct evidence of this latter effect, he has observed in biopsies of the cervix during pregnancy an unusual activity of the squamous epithelium. These views gain in weight when coupled with the growing evidence offered in the work of Schiller,[216] Hinselmann,[119] and others that areas regarded as precancerous are not as a rule in regions of maximum inflammation and may be in the midst of apparently normal epithelium.

Frequent observations of increased gonadotropic hormone in the urine of patients with cancer of the cervix are perhaps to be explained by the fact that most of these patients are in the menopause. The occasional reports of increased estrogenic hormone (Imbert, Mosinger and Bontoux,[128] Schön[218]) seem difficult to reconcile with other knowledge of the disease. Other observers have in fact failed to note (Kosakaé Ohga and Okamoto[142]) significant changes in the estrogenic excretion of cases of uterine cancer.

II. THE MAMMARY GLAND

It is in the mammary gland, however, that the most interest is centered at present and in the study of which most recent progress has been made. This can be traced directly to the fact that strains of mice are available for experimentation in which there is a high incidence of spontaneous, hereditary mammary cancer. The striking relationship between the ovarian function and the development of these laboratory carcinomas has led to a somewhat frantic effort to force human breast tumors into an identical category.

a. *Chronic Mastitis.*—The term chronic mastitis is a very loose one, having a different meaning to the clinician, to the pathologist, and to the experimental investigator with animals. To the clinician it includes practically all the diffuse benign breast conditions, manifested by pain, nodules, and discharge. To the pathologist it is a variety of conditions with four special features, namely epithelial hyperplasia, fibrosis, cyst formation, and small collections of lymphocytes and other cells suggestive of a chronic inflammation. Many workers with the lower animals apparently feel that all they need to do in order to reproduce chronic mastitis is to show some epithelial hyperplasia and possibly the cystic dilatation of a few ducts.

The production of lesions in animals, similar to the spontaneous chronic mastitis in the human being has been reported by numerous workers after the injection of one or several hormones (Goormaghtigh and Amerlinck,[103] Wieser,[261] Cramarossa[57]). In a recent series of experiments undertaken on rats Herold and Effkemann[117] have concluded that lesions similar to human chronic mastitis arise from excessive amounts of follicle hormone in the absence of corpus luteum. Others have been more hesitant in the use of the term chronic mastitis but have reported, following the protracted administration of an estrogen, atypical cellular growth preceding the development of cancer in mice (Lacassagne,[146] Burrows,[34] Bonser,[18] Gardner and others[91]). MacDonald,[173] however, working with rabbits noted a definite limit to the proliferation of ductal epithelium which could be produced by theelin and corpus luteum extract beyond which a refractory condition was set up. He concluded that these substances did not produce specific pathologic lesions such as cystic diseases or adenosis.

Turning to a review of the studies of human material, one finds that an ovarian disturbance has frequently been offered as an etiologic factor. Suggestions made in this direction are nearly a century old and several good contributions, notably that of Moszkowicz[187] in 1927, definitely preceded the isolation of the sex hormones.

Lately numerous writers, resting their case rather heavily on an analogy with the animal experiments, have proclaimed the ovarian origin of human chronic mastitis (Lewis and Geschickter,[166] Cheatle[47]).

To complicate the problem there appear to be at least two rather strongly contrasted clinical forms of so-called chronic mastitis. First, there is the type with discharge, usually of a milky or oily character, from the nipples. This is regularly associated with a stasis of secretions in the terminal portions of the ducts, giving a nodular consistency to the central area of the breast. On physiologic grounds this type might be ascribed to an excessive stimulation by one of the anterior pituitary hormones. In the second type there is instead of secretion marked pain and engorgement before the menstrual periods. With this form there may be a general hypertrophy or a nodularity usually restricted to the outer quadrants.

Based upon a clinical study of the ovarian function of a series of patients with chronic mastitis (Taylor[243]) certain points may be made. A functioning ovary is apparently essential for the persistence of the simple painful type of mastitis, because the disease rapidly improves with the menopause. This relationship is less striking when discharge from the nipple is a prominent feature, for the secretion may continue for several years after the cessation of the ovarian function. Frequent disturbances in menstruation, especially decreased flow and a prolonged interval, are present in patients with each form, but particularly with the secretory type. Cystic ovaries are often found, but changes in the endometrium rarely. Bio-assays of the blood and urine of these patients for the estrogenic hormone reveals no consistent increase or decrease in the ovarian activity.

A somewhat incomprehensible aspect of this subject has been the persistent reports of favorable results obtained by treatment of chronic mastitis with various hormones (Cutler,[64] Whitehouse,[259] Dahl-Iversen,[65] Rogers and Nathanson,[212] Gernez and Gernez,[98] Cotte,[54] Lewis and Geschickter[168]). Many observers blame the symptoms on the corpus luteum and insist on ovarian preparations free of progestin. Bérard,[13] however, deliberately gave corpus luteum and obtained good results. Geschickter and Lewis recommend estrogenic substance alone to control the formation of cysts and this plus lactogenic substance for 'adenosis.'' On the contrary Werner and Collier[257] have produced enlargement and discomfort of the breasts by giving theelin to castrated women and excellent results may certainly be obtained by reducing the patient's normal estrogen supply by radiation of the ovaries (Taylor and Brown[245]).

b. *Mammary Fibroadenoma.*—Experimental work on the fibroadenoma has centered not on the mouse, but on the rat where fibroadenoma occurs spontaneously and is easily transplantable. A number of workers have shown that the morphology of the transplanted tumor varies markedly with the sexual status of the animal. Before puberty in females and in adult males the tumor tends to be a fibroma, while in females of litter-bearing age glandular hyperplasia with a tendency to cyst formation may be prominent (Heiman and Krehbiel[113]). Changes in these tumors in pregnancy and lactation are well known (Emge and Wulff,[75] Grauer and Robinson,[104] Heiman and Krehbiel[113]). Picco[207] has reported sarcomatous changes after the injection of theelin.

The question of the actual production of new tumors by estrogenic hormone injections is somewhat clouded by the spontaneous occurrence of such tumors in a frequency said to amount to about 8 tumors in 1,000 animals. Heiman and Krehbiel,[113] however, found five such tumors among 75 animals injected with a combination of theelin and antuitrin-S or -G. Evans and Simpson[81] have also reported a high incidence of fibroadenomas in rats injected over long periods of time with anterior hypophyseal substances.

For the human fibroadenoma an estrogenic substance is perhaps also essential, for the tumor does not occur before puberty and its new development is rare after the menopause. Histologic changes in the morphology of the tumor occur with pregnancy, lactation (Hunter,[127] Kilgore,[136] Kreibig[144]), and perhaps with the menstrual cycle (Ingleby[129]). The occurrence of a high concentration of estrogenic substance in the tissues of human fibroadenomas has been reported and made the basis of a theory that the origin of the tumor is based on the ability of a local area of

breast tissue to concentrate estrogen within itself (Lewis and Geschickter[167]). Doubt has been cast on this work by the observation of Frank[85] and his co-workers that similar large amounts of estrogen may be found in the normal uterus and even in the psoas muscle.

Recent carefully controlled studies of Mohs[184] indicate very low amounts of estrogenic substance in the rat adenofibroma and even when large amounts are administered, the concentration does not arise above that in the striated muscle.

c. *Mammary Carcinoma.*—The series of experiments which have demonstrated the relation of carcinoma of the mammary gland in mice to ovarian function began with the work of Lathrop and Loeb[160] in 1913. These workers showed that in a cancer-susceptible strain the tumor incidence could be lowered and the average age of appearance raised by the prevention of breeding and by castration. This work was amplified by Loeb[161] in 1916 and corroborated by Cori[53] in 1927.

A new principle was introduced in 1928 by Murray[190] when he produced mammary cancer in male mice. Male mice, even in susceptible strains, are ordinarily entirely free from mammary cancer. Murray produced such tumors by transplanting into male mice ovarian tissue. This principle was extended by Lacassagne when he also produced mammary cancer in male mice of susceptible strains by injecting estrogenic substances.

The experiment by which mammary cancer has been produced in males of a susceptible strain has now been repeated many times (Burrows,[36] Cramer and Horning,[59] Gardner,[91, 92] and his co-workers, Bonser,[18] Suntzeff and others,[236] Korteweg[141]). In the most recent reports of Gardner and his associates[96] it is noted that mammary carcinoma may develop in male mice following the injection of a variety of estrogenic substances, theelin, equiline benzoate, ketoestrin benzoate, and hydroxyestrin.

Although the estrogenic substances are clearly an important factor in the production of mammary cancer in mice, an hereditary predisposition remains, as is shown by the greater incidence and earlier appearance of estrogen-induced mammary cancer in male mice of strains in which the females are spontaneously susceptible (Lacassagne,[148, 156] Bonser,[17] and Suntzeff and others[236, 237]). In a recently reported series of injections by Lacassagne,[156] of combined hormones into a series of mice refractory to mammary carcinoma, a variety of tumors appeared, but not of the mammary glands. Cancer may nevertheless occasionally appear in relatively resistant strains after prolonged estrin injections (Gardner, Smith, Strong and Allen[96]).

The basis for this predisposition of certain strains of mice to the development of mammary carcinoma is perhaps to be found in some constitutional peculiarity of the reproductive system. Relatively little attention has, however, been given the comparative study of the endocrine organs of these different strains. What efforts have been made have been directed chiefly toward the lengths of the estrus cycles, but although differences have been claimed (Lacassagne[157]), these have not been generally recognized (Bonser,[17] Burns, Moskop, Suntzeff and Loeb[32]).

Lacassagne[157] has in addition noted differences in the pituitaries and Cramer and Horning[60] a peculiar "brown" degeneration of the adrenals in mice of high tumor strains. Barry and Kennaway have reported some differences in the response of the thyroid gland of different strains to estrone. That variations in function of the individual animals may within a given strain affect the incidence of mammary cancer is clear from the long-recognized fact that cancer is more frequent in breeding than in virgin females (Lathrop and Loeb,[160] Bagg[10]). Whether this increased incidence is due to the irritating effects of the products of secretion or to the continuous hormone stimulation of the pregnancies is not clear. Murray has recently reduced the incidence of mammary cancer in female mice by joining them in parabiosis with a male. The effect of this experiment was to alter the estrus cycle and produce certain changes in the ovaries presumably by the introduction of the male hormone.

The finding of hormones in the tissues or the secretion of various types of diseased breast is at present of debatable significance. Substances resembling both the anterior pituitary and an estrogenic hormone have been isolated from mouse mammary carcinoma. (Dobrovolskaia-Zavadskaia and Zéphiroff.[69]) Lewis and Geschickter[168] found little or no estrogenic substance in human mammary cancer.

The evidence for an endocrine factor in human breast cancer is very difficult to evaluate.

1. The age incidence has an important bearing on etiologic theory. Approximately a third of the cases of breast cancer occur in women with a mature menstrual function. Another third occur within a ten-year period of theoretically unstable ovarian function during the five years preceding and the five years succeeding the menopause. In the older women, who represent the last third, any development of carcinoma from the ovarian hormone must presumably depend on the continued development of abnormal cellular material having its inception many years before.

2. Strong evidence now exists that there is an hereditary factor in breast cancer (Wainwright,[254] Waaler,[253] Wassink,[255] Cramer[58]). This points at least toward an intrinsic factor which is quite conceivably an inherent peculiarity of reproductive physiology.

3. Large series of statistics have shown that cancer of the breast occurs relatively more frequently in nulliparous women (Lane-Claypon[159]). This is in direct contrast with what has been observed in hereditary mouse carcinoma.

4. Lactation deficiencies occur with considerable frequency in the history of women with breast cancer (Adair[1]). The significance of this observation is not clear. Perhaps the failure to nurse is voluntary and the stasis of secretions produces irritation and cancer. Perhaps the failure to nurse is a physiologic deficiency based on some functional or structural abnormality, associated also with the cause of the breast cancer.

5. Menstrual disturbances have been reported with some frequency in young women with breast cancer (Lane-Claypon,[159] Taylor[243]). Olch[198] has noted a delay in the appearance of the menopause. These observations again may indicate a physiologic state favorable to abnormal epithelial proliferation.

6. Two or more tumors developing in separate organs of the reproductive tract decidedly suggest a common etiologic factor, and there appears certainly to be an unexpected frequency of association of pelvic and mammary tumors. Schreiner and Wehr[219] noted cancer of the breast and cancer of the female pelvic organs in 18 of 307 instances of multiple tumors. Meigs[178] noted that 10 per cent of 250 multiple tumors were combinations of a breast and pelvic growth. Taylor[244] has previously reported the special frequency of association of breast and endometrial carcinoma and isolated case reports of the coincidence of these two tumors are to be found in the literature (Seliga,[224] Esch,[80] Smith and Bartlett[234]). The association of cancer of the breast and the cervix has likewise been noted (Sitzenfrey,[232] Cordua,[52] Hellendall[114, 115]) as well as various mammary tumors with uterine fibromyoma (Taylor[243]).

7. Although the evidence for an endocrine cause for breast carcinoma is confusing, there are plenty of observations to show the effects of the ovarian hormone on already established breast cancer. There is first the widely held belief in the rapidity of growth and grave prognosis in breast cancer developing during pregnancy or lactation. Second there is the effect of suppression of the ovarian function. Bilateral oophorectomy as a method of treatment of recurrent breast cancer had a brief vogue forty years ago (Beatson[11]). This principle has been revived in recent years in the form of radiation castration (Ahlbom,[3] Hoffman,[126] Dresser[72]) which appears to be successful at times in causing a temporary regression of bone metastases. The relatively low incidence of carcinoma of the breast in women who have had their ovaries removed (Herrell[118]) suggests at least that the ovarian hormone favors carcinoma of the breast by preventing epithelial atrophy.

III. MALE GENITAL ORGANS

a. Prostate.—Striking changes occur in the male genital tracts of animals treated over long periods with estrogen. These changes affect particularly the prostatic glands and have given rise to various theories of origin for human prostatic hypertrophy. Difficulty is at once encountered, however, because the complicated embryology of the human prostate makes it difficult to relate it to the very differently constructed, although perhaps similarly functioning, glands of the lower animals.

In mice subjected to treatment by estrogenic substances there occurs especially in the so-called coagulating gland a metaplasia of the columnar to squamous epithelium, desquamation of cells into the lumen and an invasion with leucocytes (Burrows,[35] de Jongh[132, 133]). Several observers have noted that in the monkey treated by an estrogen, there develops an increase in the fibromuscular stroma, perhaps even a decrease in the epithelium, except for a stimulation or metaplasia of the epithelium of the prostatic utricle and adjacent areas of the urethra (van Wagenen,[252] Zuckerman and Parkes[283]). It may be questioned, however, how far these changes in the lower animals correspond morphologically with those observed in prostatic hypertrophy in man.

In mice these effects of estrogenic injections may be very widespread and Burrows[35] has described definite gradients of susceptibility, vestigial cysts being first affected, then the coagulating glands, next seminal vesicles and the prostate in that order. In all of these glands as well as the ejaculatory ducts the changes begin and are most marked nearest to the urethra. When estrone is withdrawn, these changes are reversible, but the return to normal begins in the peripheral portions and progresses toward the urethra. Lacassagne[148] has suggested that this selective estrogenic action may have an embryologic explanation, since portions of the dorsal wall of the urethra and its outgrowths may be derivatives of the Müllerian ducts. This might account for the similarity of this response to that of the vagina.

An interesting series of experiments have shown that these estrogen-produced changes may be prevented by giving various substances, particularly the male hormone (Korenchevsky and Dennison,[140] Rusch,[214] Overholser and Nelson,[201] Zuckerman, Zuckerman and Parkes, de Jongh[132, 133]). Burrows[42] obtained similar results with corpus luteum, but de Jongh did not. These observations have given rise to the theory that prostatic hypertrophy in man may be due to a hormone imbalance and a predominance of the estrogenic hormone (Korenchevsky and Dennison;[140] Zuckerman,[280] Niehans and others[192]). A somewhat different type of imbalance is proposed by Lower, Engel and McCullagh[171] who believe the hypertrophy due to a relative decrease in ''inhibin,'' a hormone produced by the tubular cells of the testes in relation to ''androtin,'' a substance elaborated by the interstitial cells.

Some material is undoubtedly at hand to support a theory that the estrogenic hormone is a factor in the production of benign prostatic hypertrophy even in man: (a) It is known that the human prostate responds to the estrogenic hormone. This is particularly demonstrated by the swelling of the prostates of the newborn at a time when the estrogenic hormone is known to be present in the circulation. Areas of squamous epithelium are also found in the prostates of the newborn and in young infants (Aschoff[7]; Schlachta[217]); (b) substances like the ovarian hormone undoubtedly occur in the male throughout life, as has been demonstrated by numerous workers (Oesterreicher,[197] Koch,[139] Zondek and Euler,[277] Glimm and Wadehn,[102] Bühler[26]).

Studies of the urine of men suffering from benign prostatic hypertrophy have not, however, shown an abnormal excretion of the estrogenic hormone (Owen and Cutler[202]). Other workers (Hamilton,[111] Deming[67] and Allen[5]) have failed to find estrogenic material in either the urine of patients with the disease or in the tissues of surgically removed prostates. Rusch[214] and Kundert[145] alone report that they have evidence that in men with enlargement of the prostate the male hormone is decreased in proportion to the estrogenic hormone.

The various theories of origin have given rise to a variety of endocrine treatments for prostatic hypertrophy. Castration was formerly occasionally employed (White[258]), but this operation fell into probably deserved disuse. Deming[67] and his co-workers describe a recent failure of such therapy and offer a reason for this failure, based on embryologic and physiologic grounds. Niehans[192] advocates ligation of the vas deferens, which is claimed to result in hypertrophy of the interstitial cells and thus in an overcoming of the excess of follicular over male hormone. Zuckerman[279] has reported some success in the giving of male hormone in the form of testosterone propionate. Lower, Engel and McCullagh,[171] however, have noted a 65 per cent rate of improvement in 40 cases of prostatic hypertrophy treated with ''inhibin,'' to reduce activity of the interstitial cells and prevent the excess of male

hormone. The inherent contradictions in the rationale on which these various procedures are based cast a doubt on the results reported for all of these methods of therapy.

b. Seminal Vesicles.—The effects upon the seminal vesicles which have been reported to follow estrogen injections are somewhat paradoxical. Most workers agree that an increase in weight of the seminal vesicles is due simply to an hypertrophy of the muscular walls, for the epithelium may even be somewhat reduced in amount (van Wagenen,[252] Overholser and Nelson[201] Freud[88]).

c. Scrotal hernias have been observed by several experimenters, particularly Burrows,[33] to occur in male mice treated for about ten weeks by the continuous administration of estrogenic substances. Burrows regards them as due to a relaxation of those layers of muscle which regulate the caliber of the passageway between the abdominal cavity and the scrotum.

d. Urinary retention develops in male mice treated with an estrogen and according to Burrows and Kennaway[44] is probably due to hypertrophy of the prostate. Similar observations were made by Lacassagne.[153] Chronic distention of the bladder with a secondary hydronephrosis develops in many of these animals and may terminate the experiment prematurely.

IV. EFFECTS OF THE ESTROGENIC HORMONE ON THE ORGANS OF INTERNAL SECRETION

The effects of the estrogenic hormone described to this point have been in general of a stimulating character, producing proliferation or metaplasia in the secondary organs of the male and female reproductive tracts. Besides these widely studied changes, there have been noted various reactions in the organs of internal secretion. The great majority of these effects have been observed only in animals and knowledge of their human counterparts is largely lacking. The nature of these changes is often not clear, being sometimes perhaps an hypertrophy but at other times having the character of atrophy or degeneration. These changes in the endocrine glands are perhaps themselves essential links in a chain of reactions which is set off by increases in the estrogenic hormone.

a. The Anterior Pituitary.—It has long been recognized that the ovary had a so-called inhibiting effect on the anterior pituitary gland, and it is well known that with removal of the ovaries there may occur a pituitary hypertrophy with, in some species, the appearance of so-called castration cells, enlarged basophiles containing globules of a colloid-like substance. Numerous investigators have shown that these castration changes can be prevented by the administration of estrogen (Wolfe and Chadwick[270]). When large amounts of estrogenic substance are given, there is a degranulation of the eosinophilic and basophilic cells and an increase in size and number of the chromophobe cells (Nelson;[191] Wolfe and Phelps[271]). With the administration of immense doses to rats and mice over long periods of time, there may develop adenomas of the chromophobe cells. This change was noted particularly by Cramer and Horning,[59] who observed these tumors in three, and a diffuse enlargement in eight, of twelve mice treated with an estrogen over a period of several months. The physiologic condition resulting appears to be one of hypopituitarism. Such tumors in animals have been observed after estrogen injections by several other workers, notably Zondek,[276] Burrows,[43] McEuen and others,[174] and by Selye and Collip.[225] Oberling[195] noted adenomatous areas in the hypophyses of castrated rats into which ovarian tissue had been grafted. Gardner, Strong and Smith[92] observed a chromophobe adenoma in an untreated female mouse which bore also bilateral granulosa cell tumors of the ovary and multiple mammary carcinomas.

b. Adrenals.—When estrogen is administered in large quantities to mice, characteristic effects are produced in the adrenals. These changes appear first as an increase in the thickness of the cortex with the development of a so-called x zone at its inner margin. Next there occurs an increase in the vascular connective tissue lying between the cortex and medulla and finally in the same region the accumulation of lipoid-like substances in the inner cells of the zona fasciculata which eventually coalesce to form poorly staining masses containing scattered nuclei (Burrows[41]).

Similar changes in the adrenals have been reported in less detail by other workers (McEuen and others,[174] Selye and Collip,[225] Cramer and Horning,[61] Ellison and Burch[74]). The spontaneous appearance of this degeneration in mice of a strain with a high incidence of mammary carcinoma has been observed by Cramer and Horning.[59] It perhaps represents the first anatomical demonstration of a peculiarity in the endocrine constitution of these mice predisposed to mammary cancer.

c. Testis.—In general the estrogenic hormone appears to arrest spermatogenesis, perhaps by inhibition of the anterior pituitary. Various estrogens, notably equilin, dihydroxyestrin, and to some degree trihydroxyestrin, when given to mice, cause multiplication and swelling of the Leydig cells (Burrows[38]). These become loaded with some material, probably of a fatty nature, and tend in places to coalesce and form giant cells with several nuclei. As this interstitial tissue increases, the tubular epithelium is destroyed until only a single layer of cells remains. A group of other workers have observed varying degrees of testicular atrophy in different laboratory animals. (Lacassagne,[151] Frazier and Mu,[87] Halpern and D'Amour,[109] Cramer and Horning.[60])

d. Ovary.—When large amounts of estrogenic hormone are available, follicle ripening is also delayed. This is presumably on account of the inhibiting effect of the estrogenic substance upon the anterior pituitary, for the pituitaries of animals receiving ovarian hormone are less potent, when implanted, in producing sexual maturity in immature female rats than are those of untreated animals (Leonard, Meyer and Hisaw;[163] Bialet-Laprida[16]).

Certain apprehension has been felt as to the effect of therapeutic doses of the estrogens on the human ovary, especially when given to children. Allen and Diddle[6] have shown that following large doses to immature monkeys there was an immediate slight decrease in size of the ovaries as a result of a smaller number of large follicles, but that a month later this difference between the ovaries of treated and untreated monkeys had disappeared.

V. THE SOURCES OF ABNORMAL ESTROGENIC HORMONE IN THE HUMAN BODY

From a consideration of the lesions described in the foregoing pages, several points should be clear. First, there exists ample evidence to show that immense quantities of the estrogenic substance when given to laboratory animals produce a series of changes including proliferation and metaplasia of specific tissues, some incidental inflammatory processes and various reactions in certain endocrine glands. Second, there can be found a series of lesions in human pathology which are perhaps, even probably, analogous to the experimentally produced estrogenic lesions in animals. The final proof that the latter are also due to estrogenic stimulation depends on the demonstration of some excessive activity of the estrogenic hormone in man. This has not been satisfactorily accomplished, however, for any human lesion with the possible exception of endometrial hyperplasia. For the other conditions the evidence, outside of that offered by their morphologic similarity to the estrogen-produced lesions in animals, is simply suggestive.

If one is to compare the human lesions with those of animals, it is necessary to consider sources of an abnormal hormone supply or a means by which the hormone may be abnormally effective. At the outset it must be emphasized again that the quantities injected into small laboratory animals must produce a temporary blood concentration beyond anything which may at any time conceivably exist in the human body. To this important objection several answers may be given.

1. Animal experiments are in general relatively short. It is possible that the estrogenic hormone acting in small quantities for over fifty years in the human organism may produce effects similar to those brought about by large doses in six months in the mouse.

2. It is possible that susceptible tissues or cells store or fix these substances in concentration far above that of the rest of the body. Some evidence already exists for the latter in the reported observations of large quantities of estrogen in the tissues of certain tumors.

3. Finally, the tissues in which the lesion is to develop may have simply an hereditary or acquired hypersensitivity to estrogen and hence respond excessively to normal amounts. Predisposed smooth muscle cells may become fibroids under the influence of a quite normal ovarian function. If this were the case, however, the predisposition and not the hormone must be considered the essential cause of the tumor.

Three possible sources for an excessive supply or abnormal type of estrogenic hormone in the human organism may nevertheless be considered.

1. Origin from follicles: The cystic ovary has been implicated by clinicians and pathologists in a variety of lesions, including endometrial hyperplasia, endometriosis, fibromyoma and chronic cystic mastitis. In spite of this the functional significance of the cystic ovary is all but unknown. In some types the epithelium of the cysts is degenerate and the fluid contains little or no hormone. In others the granulosa and thecal cells are well preserved and the cyst fluid contains estrogen (Philipp,[206] Moulonguet,[188] Metz,[179] Adair[1]) and rarely an anterior pituitary-like hormone as well (Siegmund,[230] Brindeau, Riehl, Hinglais and Hinglais,[25] von Probstner,[210] Mozzetti-Monterumici[189]).

The cause of these functional cysts of the ovary is also little understood. There still exists a school believing that the cause is a local one in the form of a hyperemia or congestion resulting on the one hand in the speeding up of follicle ripening, and on the other in an eventual fibrosis which makes rupture of the follicle mechanically difficult. Both experimental and clinical evidence on the other hand point also to the anterior pituitary gland as a factor in at least certain types. Cystic conditions can be produced in the animal ovary by the injection of the anterior pituitary hormone or the implantation of the gland (Engle,[77] Selye and Collip[225]). Injection of the anterior pituitary-like hormone of pregnancy into women some days before an expected laparotomy has resulted in cystic and degenerative changes in the ovaries (Zondek,[275] Mandelstamm and Tschaikowsky,[176] Geist,[97] Hamblen and Ross[110]). The small cysts discovered in the ovaries of the newborn have been explained as the result of stimulation by the placental hormone reaching the fetal circulation or of the infant's own pituitary activity (Spivack[235]). Finally cystic ovaries have been noted in patients suffering from various types of intracranial lesions in which functional disturbances of the anterior pituitary were probable (Cushing and Davidoff,[63] Kraus[143]). The theca lutein cysts associated with hydatidiform mole and chorioepithelioma are probably also examples of effects of high concentrations of pregnancy hormone.

Thus it appears that the cystic ovary is a possible indicator of anterior pituitary activity, and a possible sign of abnormal ovarian function. Nothing could be more important in the elucidation of the lesions said to be due to an ovarian disturbance than a method of determining the functional significance of certain ovaries, particularly those with multiple small cysts.

2. Origin from ovarian tumors: The cases of granulosa cell tumor with endometrial hyperplasia give perfect examples of a demonstrable source and demonstrable effect of estrogenic substances. These cases are of course not common, but it is possible that small tumors or less organized cell collections similar in origin and in function to the granulosa cell tumors may more often be the source of hormone.

3. An extra-ovarian source: The origin of estrogenic substances outside of the ovary is easily demonstrable. First it is known that males excrete definite amounts of estrogenic substance and secondly it has been shown that women continue to have estrogenic material in the blood and urine after the menopause, after radiation of the pelvis, and even after surgical removal of the ovaries (Frank and others[85]).

Recent work on the chemistry of the ovarian hormones has shown their relationship on the one hand to cholesterol and the bile acids (Rosenheim and King,[213] Wieland and Dane,[260] Butenandt,[45] Dodds[70]) and on the other hand to a series of derivatives of tar which are actively carcinogenic (Cook, Hewett and Hieger,[51] Cook, Dodds, Hewett and Lawson[49]). From these advances in the chemistry of these substances two theories deserve consideration: (1) Estrogenic substances may arise in association with the metabolism of cholesterol and the bile acids, quite out-

side of the ovary, and so be effective in males as well as in females after the menopause. (2) Disturbances in the normal chemistry of either the sex hormones or of the bile acids might result in the formation in the body of chemically related carcinogenic substances. The latter possibility has already given birth both to hypothesis and to caution against premature judgment (Cook and Dodds,[48] Dodds,[71] Loeb,[169] Thomson[248]).

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Selected Abstracts

Physiology of Pregnancy

Samuels, J.: An Exact Method of Determining Ovulation and Pregnancy, J. Obst. & Gynaec. Brit. Emp. **44:** 1036, 1937.

The author discusses previous experimental work in which by means of an abdominal window he observed directly the tubes and ovaries of rabbits during various phases of the estrus cycle. He noted that the tubal fimbriae were dragged across the ovary to and fro. This phenomenon is explained by contraction of the smooth muscle and mesotubarium. The ovary was seen to shift its position cranially and caudally due to rhythmic contractions of the muscular ovarian ligament, rotating on the long axis so that its various surfaces faced the fimbriae and the ostium abdominale.

With the monkey a laparoscope was utilized during various phases of the cycle. During the interestrual phase the tube lay laterally convex, moderately twisted and bow-shaped so the pars ampullaris and pars isthmica approached each other and the infundibulum turned to face the ovary. Minor movements were observed by which the fimbriae were dragged to and fro across the ovary. The ovary was noted to be displaced cranially and caudally as well as rotatory. These phenomena are explained by the action of smooth muscle in the mesotubarium and ovarian ligament.

A series of observations in man are reported. At laparotomy for associated conditions the ovary was injected with a drop of lipiodol under the tunica albuginea at the upper and lower poles and in the free border prior to closing the abdomen.

Subsequently these patients were followed with serial roentgen films to ascertain the position of the opaque indicators and also to determine the reaction of the ovary to dye-filled tubes. These observations demonstrated a definite alteration in the position of the ovary, and in some cases the relative anatomic position of the tube

and ovary was determined. These studies demonstrated displacement of the ovary cranially and caudally and rotation of the ovary on long axis. The ostium of the tube was noted projected at first over the upper pole of the ovary and subsequently over the uterine pole.

Suction of ova into the tubes, set up by cilia and also due to rhythmic contractions of the tube, is discussed.

The author notes that the ligaments of the human adnexa contain a great amount of smooth muscle and concludes that ova are transferred directly from the ruptured follicle to the tube in a manner similar to that noted in experimental animals.

S. J. SOULE.

Samuels, J.: Early Diagnosis of Pregnancy, München. med. Wchnschr. **84:** 1323, 1937.

The writer presents a direct spectroscopic method of diagnosing early pregnancy. He employs an instrument, called a cycloscope (spectroreductometer), which determines the reduction of oxyhemoglobin, which in nonpregnant individuals takes about 145 seconds. Pregnancy is diagnosed when the cyclic variations which are observed in nonpregnant individuals are absent. He claims that the cycloscope will, in every case, diagnose a pregnancy seven or eight days after conception or twelve days before the time of the next menses.

The test is rapid and simple and can be carried out by any physician.

J. P. GREENHILL.

Patterson, Jocelyn: The Chemical Diagnosis of Early Pregnancy, Brit. M. J. **2:** 522, 1937.

A biochemical test for the diagnosis of early pregnancy is described which is based upon bacterial splitting of oestriol glycuronide and the subsequent development of the oestriol color reaction with phenolsulphonic acid. Of 65 cases, in all except one, the results coincided with those of the Friedman reaction.

The advantages and disadvantages of the test as compared with other biologic tests are discussed.

F. L. ADAIR AND S. A. PEARL.

Schneider, Bernhard, and Cohen, Armand: Nonspecificity of Gonadotropic Factor of Pregnancy Urine Intradermally, J. A. M. A. **109:** 115, 1937.

The results obtained with antuitrin-S, injected intradermally, in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders. One hundred eighteen tests were done on 95 females and 23 males. The observations made would indicate that 11 individuals were nonpregnant and 107 were pregnant. Actually, however, there were only 21 pregnancies.

GROVER LIESE.

Gill, A. Morton, and Howkins, John: The Antuitrin S Intradermal Pregnancy Test, Brit. M. J. **2:** 1069, 1937.

The authors attempted to substantiate the favorable results reported by early investigators of the antuitrin-S intradermal pregnancy test. Male medical students, and pregnant and nonpregnant females were studied. The cutaneous reactions were read at one-half, one, and two hours. The results from antuitrin were so palpably inaccurate for the first 147 cases that the investigation was abandoned at that point.

Thinking that perhaps the foreign protein rather than the specific hormonal content accounted for some of the skin reactions, an additional 41 individuals were tested with inactivated antuitrin-S. The results from this group were as fallacious

as those obtained with active antuitrin-S. The authors concluded that this test for pregnancy, though enthusiastically acclaimed by some, has proved valueless in their hands.

F. L. ADAIR AND JOHN A. HAUGEN.

Abramson, Hurwitt, and Gerson: Relaxin in Human Serum as a Test of Pregnancy, Surg. Gynec. Obst. **65:** 335, 1937.

A substance in the corpora lutea of sows and the serum of pregnant rabbits, which was capable of producing symphyseal relaxation in guinea pigs in normal or artificial estrus, was first described by Hisaw and named relaxin.

Although slight to moderate degrees of relaxation can be produced in guinea pigs by large doses of theelin, the separation is greatly increased by a small additional dose of relaxin. Pelvic relaxation in pregnant animals is therefore not solely a theelin effect.

A procedure has been developed for concentrating human blood serum taken from women in the first half of pregnancy which has acted on guinea pigs in a manner similar to that of relaxin. Symphyseal relaxation in guinea pigs in artificial estrus was produced by the sera of 15 consecutive women in the first half of pregnancy. The serum of 1 woman in the eighth month of pregnancy and that of 2 nonpregnant women and of 1 male were ineffective.

It is believed that pelvic relaxation during pregnancy is facilitated by, or at least in part is due to, the hormone relaxin in the human species as well as in many other mammalia. As a routine test of pregnancy this procedure is deemed impractical.

WM. C. HENSKE.

Crew, F. A. E.: The Aschheim-Zondek Test in the Puerperium, Brit. M. J. **1:** 363, 1936.

There is no general agreement as to when, following pregnancy and normal parturition, the Aschheim-Zondek test first gives a permanent negative result. Aschheim and Zondek state that the reaction may disappear as early as five days after childbirth, and regularly ceases after eight days. Mazer and Edeiken believe that two weeks is the possible limit, while Hamburger states that the hormone content abruptly falls in the first twenty-four hours after delivery and in the succeeding twelve days gradually drops below any demonstrable level. Mack and Agnew found positive results two to seven days following parturition in four cases. Robson states the test is positive "about a week or ten days" after living products of conception are present.

The author followed a series of 50 cases daily and reports his results. Only 2 patients gave positive tests seventy-two hours after parturition and ninety-six hours after delivery all cases were negative. Five cases were negative seven hours after delivery. Out of these one gave a weekly positive test twenty-four hours after, and the other four continued consistently negative.

The conclusion, therefore, is that the Aschheim-Zondek test invariably yields a definite and presumably permanent negative result ninety-six hours after normal and complete parturition. The test may be adopted on the fifth day of the puerperium as a means of determining retained living products of conception.

F. L. ADAIR AND S. A. PEARL.

Kehrer, E.: Endocrine Syndrome During Pregnancy and After the Puerperium, Ztschr. f. Geburtsh. u. Gynäk. **110:** 105, 1937.

The author states that there usually is a hypertrophy of most of the endocrine glands during pregnancy, more pronounced perhaps in the pituitary with the hypertrophy of eosinophilic cells which are the cause of the signs of acromegaly that are so frequently observed during the latter half of pregnancy. The increase in size of the pituitary body may indirectly result in diabetes insipidus. After the puerperium, symptoms of pituitary adiposity may appear associated with amenorrhea. Thyroid insufficiency may complicate the pituitary deficiency at a later date.

Kehrer believes that diabetes mellitus develops primarily after the puerperium and states that the disease is more common in parous than in nonparous women. He further believes that septic puerperal processes are not uncommonly followed by fibrous atrophy of the pituitary, thyroid, ovaries, and adrenals.

EUGENE S. AUER.

Celentano, Pasquale: The Proteolytic Ferments of the Hemocytes in Pregnancy, Archivio di Ostetricio e Ginecologia **41:** 685, 1935.

The proteolytic ferments of the leucocytes were studied in 26 pregnant women. It was found that there was an increase in the tryptic power, and furthermore a peptic enzyme, not present in the normal woman, was noted. These findings can be explained by the presence in the blood of a greater amount of protein of alimentary origin not completely digested in the intestine.

J. M. PIERCE.

Fernandez-Ruiz, César: Calcium and Magnesium Balance During Pregnancy, Med. ibera **1:** 102, 1936.

The author found that during pregnancy an increase in magnesium is accompanied by a reduction in calcium. He believes that magnesium has an inhibitory action upon the deposition of bone-forming substance.

F. L. ADAIR AND J. SUAREZ.

Effkemann, G.: Changes in Fat Metabolism Before the Onset of Labor in Normal Pregnancy, Arch. f. gynäk. **159:** 718, 1935.

The author describes the incretory changes which take place in the pregnant woman just before labor sets in and gives his own findings regarding changes in fat metabolism during this period. He finds the fatty acid content of the blood during the several days preceding the onset of labor higher than it was during the second half of pregnancy. His values ranged from 700 to 850 mg. per 100 c.c. of blood. The acetone bodies were likewise increased during this period. The acetone values in pregnant women average 240 mg. and begin to increase about six days before labor sets in, finally reaching values of 640 mg. in the daily urine. The hypophyseal hormone regulating fat metabolism is also slightly increased during this time.

RALPH A. REIS.

Fronticelli, Enrico: The Maternal, Fetal and Placental Blood Urea Index, Clin. ostet. **14:** 641, 1935.

From a study of the urea content of the blood of the mother, fetus and placenta, immediately after delivery, the author concludes that the maternal nitrogen content of the blood is lowered during labor; the fetal nitrogen content is independent of the maternal nitrogen content and is lowered a day or two after birth. The placental and fetal nitrogen contents are almost alike. The function of the placenta, in regard to the fetal nitrogen content, is like that of the kidneys, in the sense that it maintains the blood nitrogen index within physiologic limits and conveys urea to the maternal blood.

AUGUST F. DARO.

Traverso, G. L.: Study of Erythrocyte Volume During Pregnancy, Folia Gynaec.-Demograph. (Genova) **34:** 449, 1937.

In a study of the blood of 322 pregnant women the author found that the red blood corpuscles obey the laws of hematic compensations. That is, the increase of volume of a single red corpuscle corresponds to the decrease of the number of elements in the unit of volume of blood and vice versa. Since his findings show a progressive decrease of volume of the single element from the beginning of pregnancy up to the fourth month with permanence of the minimum volume from the

fourth to the seventh month, and furthermore show progressive increase during the eighth and ninth months, without having the said volume reach that of the normal isonumeric red corpuscles, the author suggests that pregnancy stimulates microcytic activity.

MARIO A. CASTALLO.

Landt and Benjamin: Cardiodynamic and Electrocardiographic Changes in Normal Pregnancy, Am. Heart J. **12**: 592, 1936.

Observations were made on 19 normal pregnant women throughout the course of their pregnancy and puerperium. The study included correlation of clinical, cardiodynamic, and electrocardiographic changes. Final examination was made approximately two months after delivery. The study indicates that pregnancy definitely places a burden on the cardiocirculatory system. In the normal woman this burden can be compensated by calling on the reserve capacity of this system. The method of compensation is both mechanical and physiologic. The electrocardiographic changes during pregnancy may be interpreted definitely on the basis of mechanical shifting of the heart, usually expressed in a left axis deviation in the electrocardiogram. The normal woman who does not develop any untoward signs or symptoms during the course of pregnancy shows a normal clinical, cardiodynamic and electrocardiographic picture six to eight weeks after delivery.

J. P. GREENHILL.

Burwell, C. Sidney: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy, Am. J. M. Sc. **195**: 7, 1938.

The demonstrated phenomena of the circulation in pregnant women plus the evidence offered by the structure of the placenta lead to the conclusion, that the changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) Obstruction to venous return by the enlarged uterus; (2) an arteriovenous leak through the placenta.

J. THORNWELL WITHERSPOON.

Piccone, L.: The Larynx in Pregnancy, Folia Gynaec.-Demograph. (Genova) **31**: 131, 1935.

The author refers to previous studies of this question. His histologic studies on dogs and rabbits demonstrated common changes in all the organs of the body and certain slighter modifications limited to special areas, particularly glottis and epiglottis.

In the larynx, can be observed new formation of blood vessels, a hyperemia of the vessels themselves, together with a more or less marked lymphatic infiltration. The connective tissue is found to be edematous with lymphatic spaces greatly dilated.

These changes were not found in the nonpregnant control animals nor in animals subjected to hormonal injections.

These processes, the author feels may explain the rapid progress of laryngeal tuberculous lesions during pregnancy.

MARIO A. CASTALLO.

Abbott, A. Clifford, and Prendergast, James: The Histology of the Thyroid Gland in Pregnancy, Canad. M. A. J. **34**: 609, 1936.

The three principal beliefs regarding the thyroid gland in pregnancy are: (1) that the thyroid gland becomes hyperplastic during pregnancy, (2) that the thyroid gland becomes hypoplastic or colloid in nature during pregnancy, (3) that there is no change in the histology of the thyroid gland. In general, American observers favor the hyperplastic theory, while continental workers believe that there is no change or that the gland becomes colloid in nature. As yet, there is no definite proof of pathologic change.

The authors studied the thyroid glands of a large number of pregnant animals. They believe that this gland has a wider range of physiologic variation than has been acknowledged heretofore. The evidence accumulated points toward a slight increase in activity of the gland during pregnancy, which is entirely physiologic in character. This increased activity in the animals was most pronounced in the earlier months of pregnancy.

To prove changes one must have positive knowledge of the gland before the onset of pregnancy as well as afterward. In this district 30 per cent of the young women have enlarged thyroid glands before pregnancy, which corresponds very closely to the number reported during pregnancy. Furthermore one must differentiate between enlargement due to lack of iodine and enlargement due to pregnancy.

H. CLOSE HESSELTINE.

Traut, Herbert F., and McLane, Charles M.: Physiological Changes in the Ureter Associated with Pregnancy, Surg. Gynec. Obst. **61**: 65, 1936.

The normal ureter of the nonpregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded.

In the majority of 34 patients studied, this rhythmic peristaltic activity is definitely altered by pregnancy in varying degrees. There is a diminished amplitude of the peristaltic wave, commencing in the third month of pregnancy, but reaching its peak during the seventh and eighth months. After the fifth month the number of patients showing diminished ureteral response exceeds those showing normal activity. During the last month of pregnancy there seems to be a definite return of muscular irritability as expressed by the measurement of peristalsis and response to stimulation.

This diminished peristaltic activity of the ureters in pregnancy cannot be explained on a basis of passive dilatation. Dilatation of the ureters during pregnancy is probably in great part dependent upon the atony of the ureters due to some unexplained chemical factor.

WM. C. HENSKE.

Traut, McLane, and Kuder: Physiological Changes in the Ureter Associated with Pregnancy. The Relationship Between Atony and Dilatation of the Tract, Surg. Gynec. Obst. **64**: 51, 1937.

New evidence is brought to light indicating that the physiologic dilatation of the ureter in pregnancy is not due to the weight of the pregnant uterus primarily, although this is undoubtedly a contributing factor. The characteristics of the ureteral atony are thought to be similar in many respects to that affecting the uterine musculature. It is suggested that the phenomena in the two organs may have a similar etiology which is unknown.

The ureteral dilatation is roughly proportional to the degree of atony and both appear and disappear at similar times with regard to the course of pregnancy.

Dilatation and atony appear in the third month and are progressive to the seventh month of pregnancy. During the last two months, there is a marked increase in motility, accompanied by a moderate decrease in the dimensions of the tract. Following delivery, atony is again marked until the third week, subsequent to which motility returns rapidly to normal levels, which are usually attained during the sixth or the seventh week post partum. Dilatation of the tract decreases progressively after delivery and reaches practically the normal values at the seventh week of the puerperium.

WM. C. HENSKE.

de Snoo, K.: The Drinking Child in Utero, Monatschr. f. Geburtsh. u. Gynäk. **105**: 98, 1937.

De Snoo performed experiments whereby he sweetened liquor amnii to entice babies in utero to drink large amounts of liquor. He also attempted to treat babies in utero directly by introducing medication into the amniotic sac. Since 1922 he has

treated more than 20 babies in this way, and he is convinced the procedure has practical value. His first attempts were to reduce polyhydramnios by sweetening the liquor amnii with saccharin to make the baby swallow large amounts of fluid. By this means he succeeded in overcoming polyhydramnios, enabling women to carry their pregnancies to full term. In these cases the babies were somewhat edematous at birth and showed saccharin in the urine.

In some cases the author injected methylene blue into the amniotic sac. This dye was absorbed by the intestinal tract of the baby and eventually found its way into the mother's urine which stained blue. Since the membranes do not absorb methylene blue, we have here a means of determining whether or not a baby has swallowed water. The author found that the urine did not uniformly stain blue, but there were intervals when the urine was clear. The urine stained deepest when the child was most active. The author therefore believes that the child sleeps in utero for a few hours at a time and on awakening moves about and drinks water.

The procedure recommended by de Snoo can be used to determine whether or not a baby in utero is alive. There are two exceptions to this however. The first is the child who cannot drink, as in many cases of anencephalus and the second is the baby in whom the imbibed water cannot be absorbed, as in atresia of the esophagus and pylorus.

The author's experiments prove that excessive liquor does not come from the fetal kidneys but from the placenta and amniotic epithelium.

J. P. GREENHILL.

Sontag, L. W., and Wallace, R. F.: Changes in the Rate of the Human Fetal Heart in Response to Vibratory Stimuli, Am. J. Dis. Child. **51**: 583, 1936.

That the human fetus is capable of perceiving sound vibrations has been shown by reports as the following: A case of Forbes and Forbes of a woman who while attending concerts noticed increased fetal movements whenever the audience applauded. Peiper reported increased fetal movements following certain sound stimuli. Ray observed fetal movements in response to the sound of two boards clapped together. Similar observations had previously been recorded by Sontag and Wallace.

In this new study the same authors investigated in a total of 217 experiments on 8 women in various stages of pregnancy the possible effect of vibratory stimuli on fetal heart rate. They found such an increase, averaging about 11 beats per minute, in response to vibratory stimuli applied to the mother's abdomen with a frequency of about 120 beats to the second. The rate of increase was the larger the nearer term the pregnancy was. They conclude that response to vibratory stimulation thus is expressed not only in increase of fetal movements but as well of fetal heart rate.

HUGO EHRENFEST.

Strachan, Gilbert I.: Some Problems in Antenatal Supervision, Lancet **2**: 665, 1936.

Obviously antenatal care is to determine any abnormalities and to correct them. Even with the institution of this service the maternal mortality has not been appreciably altered. Pelvimetry has only a limited value due to the fact that soft tissue alters the size of the birth canal. The determination of the diagonal conjugate is inaccurate. The more important matter in borderline pelves is the size of the baby in relation to the maternal passage and its presentation. Occipitoposterior positions may suggest disproportion. Trial labor will determine this more exactly.

One cannot predict in advance the position of the presenting part, the amount of molding, strength of uterine contractions or degree of joint relaxation. Breech presentation in the primigravida may become a difficult problem. External version may rectify the condition, yet this procedure may result in separation of the placenta.

Hemorrhages are usually unpreventable, but toxemias may be discovered early. A failure to decrease the maternal mortality rate may be the result of unnecessary

operative measures, such as inductions of labor and cesarean sections. All operative procedures are associated with a certain risk.

It is important to evaluate carefully the past obstetric history. Antenatal care will contribute to the lowering of the maternal death rate especially when guided by sound judgment, and dexterity and patience in parturition.

H. CLOSE HESSELTINE.

Bak, M.: The "Cold Test" During Pregnancy, Labor and the Puerperium, Monatschr. f. Geburtsh. u. Gynäk. **105**: 24, 1937.

During pregnancy, the "cold test" (dipping of hands into cold water) produces an average elevation in blood pressure of about 20 mm. Hg. Even among healthy gravidas there are variations in the reaction. In women who have a tendency to develop the toxemias of pregnancy and in those who have had such toxemias, there is a very rapid and pronounced rise in blood pressure, and this elevation is sustained for a longer time. In women who have the toxemias of pregnancy, the cold test produces only a slight increase in the blood pressure. It may remain constant or it may even fall. The results obtained with this test during pregnancy, labor and the puerperium do not vary from one another.

J. P. GREENHILL.

Evans, Arwyn: Variations of Weight During Pregnancy, Brit. M. J. **1**: 157, 1937.

The variations in weight of 211 patients, 52 of whom developed toxemia, have been investigated and analyzed by the author.

The average gain of the toxemic patients was found to be definitely more than that of the normal patients. Moreover, a sudden abnormal increase in weight was of great value in foretelling a toxemia; 63 per cent of the patients who gained more than 8 pounds in one month became toxemic, whereas the incidence of toxemia in those patients with a normal monthly gain was only 0.9 per cent.

If a patient gained more than 5 pounds in a particular month it did not invariably signify that a toxemia would develop, but 98 per cent of the toxemic patients showed this abnormal gain.

This abnormal increase in weight appeared, on the average, one month before the albuminuria, and was as a rule an earlier sign than a raised blood pressure.

The type and duration of labor did not appear to be affected by increased weight of the mother. Loss of weight a few days before labor was noted in only 36 per cent of the cases.

It was concluded that systematic weighing of patients during the antenatal period is of definite value in foretelling, and perhaps avoiding, the toxemias of pregnancy.

The average increase in weight during pregnancy is 16 to 18 pounds, and the monthly gain during the second and third trimesters is normally between 2 and 4 pounds.

An increase of 5 pounds or more per month is suggestive of an impending toxemia, the probability of its occurrence varying directly with the amount of the sudden increase.

Every patient should be weighed regularly throughout pregnancy, and be instructed to consult her doctor if the monthly gain is 5 pounds or more.

F. L. ADAIR AND S. A. PEARL.

Wahl, F. A.: Are Children Larger and Does Pregnancy Last Longer Than Formerly? Deutsche med. Wchnschr. **63**: 769, 1937.

Measurements on more than 6,000 premature newborn infants revealed the length-weight quotient averages 51.5 cm.: 3,400 gm. A comparison of these values with those formerly determined and accepted indicates that mature infants are longer as well as heavier than was formerly assumed. Regarding the duration of pregnancy, the author says that former studies in 4,000 cases, which have been corroborated by more recent studies in 5,000 cases, indicated that, counting from the last menstruation, pregnancy lasts from 284 to 285 days; that is, from four to

five days longer than was formerly assumed. He suggests that the comparatively greater length and weight of the newborn infant are due to the fact that gestation lasts longer than formerly. He also discusses the length of pregnancy with regard to the date of conception, pointing out that, on the basis of his own observations and of the results obtained by Knaus, Ogino, and others with regard to the term of ovulation, the average duration of pregnancy (counted from conception) is from 273 to 274 days. After directing attention to similar phenomena, such as the increase in the average height and in the life expectancy, the author cites several, particularly social-economic environmental, factors to which these changes may possibly be ascribed.

J. P. GREENHILL.

Rucker, P.: Effect of Diet on Outcome of Pregnancy, Kentucky M. J. **35**: 329, 1937.

In the opinion of the writer, the Prochownik diet is a distinct help in the management of labor of a patient with a contracted pelvis. A patient on this diet has a tendency to go into labor prematurely, and the labor is distinctly shorter. Some 200 babies of mothers on a Prochownik diet were of average length but had less than average weight. There was no evidence of toxemia or kidney damage in any of the patients, and there was no indication of harm to the baby.

J. P. GREENHILL.

[It might prove interesting to add here the following data: When Prochownik, in 1889, first proposed a specific diet for patients with minor pelvic contractions he was not aware of the fact that similar suggestions had been made by several writers as early as the end of the eighteenth century. By the experience gained with *three* patients he felt justified in recommending for the last six weeks of pregnancy a diet poor in liquids and carbohydrates and rich in proteins, in general resembling the diet usually prescribed for diabetic patients. The results obtained in these three cases to him seemed most satisfactory. The three children showed no evidence of having been harmed by the changed and restricted food supply of their mothers, and exhibited all the characteristics of full maturity. They were of average length with normal skeletons, all bones apparently as hard as normally seen. Striking in some of these children was only the obvious deficiency in fat tissue.

Readily acknowledging that the head dimensions were found normal, the skull bones of normal hardness, Prochownik offered the following explanation for his observation, that in these three instances labors subsequent to the diet seemed easier in comparison with preceding ones: *A striking thinness and slackness of the skin covering the head, due to the absence of fat tissue, increases the mobility of the skull bones against each other, facilitates molding, and thus permits an unusual degree of compression of the head during labor.*]

HUGO EHRENFEST.

Murless and McLaughlin: Does Superfoetation Occur? Brit. M. J. **1**: 1309, 1937.

The authors present the case of a multipara with a long and interesting obstetric history in whom six successive stillbirths were followed by the delivery of two full-term babies ninety-two days apart. The explanation suggested is superfetation.

Many similar cases are described in the old literature but none in recent years. The condition is rare but does occur. Some of the old literature is outlined in which evidence is presented that ovulation may occur during pregnancy; that cases of abortions of fetuses differing widely in size and development occur frequently; and that superfetation has been induced in animals.

F. L. ADAIR AND S. A. PEARL.

Kelly and Woods: A Quantitative Study of the Friedman Test for Pregnancy, J. A. M. A. **108**: 615, 1937.

The presence of one or more *ruptured* follicles in one or both ovaries as well as the presence of several *unruptured hemorrhagic* follicles in both ovaries constitute a positive reaction for this test.

Unruptured follicles are red; black follicles of all sizes have no significance and must be disregarded. Corpora lutea visible to the naked eye do not develop within forty-eight hours, nor can they be seen with the low-power binocular microscope. In many cases the low-power microscope is necessary in order to reach a correct decision.

The common modification of the Friedman test is satisfactory, though the original Friedman technique gives better quantitative results. One injection of 10 c.c. of urine with examination in thirty-six hours is not nearly as successful as the double injection, and better results would be obtained with two injections and examination in forty-eight hours. Rabbits weighing more than three pounds will give better results than those weighing less, and three pounds is a safe minimum. It is safer not to use urines with a specific gravity of less than 1.008.

GROVER LIESE.

Thomson and Cohen: Studies on the Circulation in Pregnancy, Surg. Gynec. Obst. **66:** 591, 1938.

Vital capacity and related observations on 31 normal pregnant women (21 primiparas, 10 multiparas) comprise the material for this report.

Since the vital capacity does not, as commonly supposed, decrease spontaneously during normal pregnancy, a significant decrease during pregnancy must be explained by some pathologic state.

The ''dyspnea of pregnancy'' depends largely on the ratio between vital capacity and pulmonary ventilation. A large increase in pulmonary ventilation with only a slight increase in vital capacity to accompany it, would lead to the development of dyspnea. This is precisely what happens in pregnancy. The pulmonary ventilation increases considerably, an average 57 per cent increase.

The irritability of the ''respiratory center'' is heightened. Finally it is reasonable to speculate that the altered lungs of pregnancy may, through the mechanism of reflex dyspnea from the congested lungs, lead to increased ventilation and dyspnea.

The vital capacity in normal pregnant women is within the limits set as normal for nonpregnant women. During the course of normal pregnancy, the observed vital capacity usually remains constant or shows a slight increase. The observed vital capacity decreases after delivery in most cases. There is an increase in the subcostal angle during pregnancy, with a post-partum decrease. The increase in vital capacity during pregnancy parallels closely the increase in subcostal angle value, as does the post-partum decrease. The change in vital capacity in pregnancy is associated with alterations in the size and shape of the chest. The increase in the observed vital capacity in pregnancy is not proportionately as great as the increase in body weight and approximate surface area. The vital capacity in the lying position during pregnancy is approximately 5 per cent less than in sitting and standing positions, but changes in a similar way. The vital capacity in the standing position during pregnancy is slightly higher than in the sitting position. Age and parity have no apparent effect on the vital capacity in pregnancy.

WILLIAM C. HENSKE.

Gerdes and Boyden: The Rate of Emptying of the Human Gall Bladder in Pregnancy, Surg. Gynec. Obst. **66:** 145, 1938.

Detailed cholecystographic studies of 21 healthy gravid women, following intravenous administration of iso-iodeikon, have shown that while the gallbladder could be visualized in 18 of them, 4 of the 5 that were tested both ante partum and post partum exhibited improved concentration of the dye six to eight weeks after parturition. This finding points to a gestational alteration in the concentrating power of the gallbladder wall.

The rate of emptying of the gallbladder, as testified by the modified Boyden meal, is not significantly different from the normal rate during the first three months of pregnancy, but in the second and third trimesters there is a marked retardation in flow, the mean discharge in 13 cases being only 52 per cent (at forty minutes post cibum) as against the normal nulligravida mean of approximately 73 per cent.

Even more significant is the comparison of the rate of emptying in the same individual before and after parturition. The mean discharge at forty minutes post cibum in 5 patients subjected to this test, was only 38 per cent during pregnancy as against 71 per cent, six to eight weeks post partum.

On the basis of Westphal's peptone and pilocarpine experiments with gravid women, this initial delay in the response to a motor meal is attributed to a hypertonic condition of the sphincter choledochus, i.e., to a physiologic dyskinesia reflecting the changed hormonal content of the organism in pregnancy. The evidence indicates that this delay is a lengthening of the normal "two-minute pause" that usually occurs immediately after the first rise in tonus of the gallbladder wall following ingestion of food.

The resulting biliary stasis accounts for the distended gallbladders found at term in 75 per cent of Potter's large number of cesarean sections and for the thick, tarry contents of gallbladders at term which are characterized by a low bile-salt (and a high cholesterol) concentration that is comparable only to that found in vesicles with a damaged wall. In conclusion, it is believed that the stasis of pregnancy sets the stage for the sequence of events which results in the greater incidence of gall stones among women that have borne children.

WILLIAM C. HENSKE.

Hirst, John Cooke, and Strousse, Flora: The Origin of Emotional Factors in Normal Pregnant Women, Am. J. M. Sc., **196:** 98, 1938.

So-called "normal pregnant women" might well be highly abnormal, and even if they are not they are anxious to a degree beyond that of the so-called "normal" non-pregnant female. Types of anxiety are influenced by the social and economic group from which they are selected. In the group of 50 cases adequately followed up after childbirth, even though the economic situation was unchanged, there was a definite lessening of anxiety in 40 cases. The authors make a plea for at least one experienced dispensary staff attendant at each prenatal clinic, and for a note of the nervous status on each obstetric record. All women showing phobias or even marked anxiety during pregnancy should receive sympathetic encouragement by the chief of service, and if necessary, psychiatric advice. Among 100 presumably normal pregnant women 75 per cent showed anxiety related to economic stress; 7 per cent to their husbands, 10 per cent to other members of their families; while 16 per cent showed definite phobias concerned with fear of ill-health or death, or of the child being defective.

J. THORNWELL WITHERSPOON.

Items

Chicago Gynecological Society

The following officers were elected for the ensuing year:

President:	David A. Horner
President-Elect:	Julius E. Lackner
Vice-President:	Harold K. Gibson
Secretary:	Edward Allen
Treasurer:	George H. Gardner
Pathologist:	John I. Brewer
Editor:	William B. Serbin

Central Association of Obstetricians and Gynecologists

The Tenth Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held at the Hotel Radisson in Minneapolis on Thursday, Friday, and Saturday, October 6, 7, and 8, 1938, in connection with the Minnesota Society of Obstetrics and Gynecology. Dr. Jennings C. Litzenberg will be the honored speaker.

Washington Gynecological Society

At the Annual Meeting, held May 9, 1938, the following officers were elected:

President:	Joseph J. Mundell
First Vice-President:	Herbert P. Ramsey
Second Vice-President:	Richard L. Silvester
Treasurer:	George Nordlinger
Historian:	John W. Warner
Secretary:	H. J. Russell McNitt
Council:	Howard F. Kane
	Leon A. Martel
	Albert E. Pagan
	William J. Stanton
	Jerome F. Crowley

International College of Surgeons

The Second National Assembly of the International College of Surgeons will be held in Philadelphia, Pa., with the headquarters at the Bellevue Stratford Hotel on October 13 and 14, 1938. All members of the medical profession of good standing are cordially invited to attend the scientific program and various clinics. There will be no registration fee.

Assembly of Laboratory Directors and Serologists

A meeting, under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis, with Surgeon General Thomas Parran, Chairman, is scheduled for October 21 and 22, 1938, at Hot Springs National Park, Arkansas.

The aims and purposes of the assembly will be to consider means and methods to improve and to make more generally available the serologic tests, which are so important in syphilis control work. Tentative arrangements call for the presentation of the program in four sections.

The first section will consider the need for adherence to conventional technic in the routine performance of reliable serodiagnostic tests. This subject will be considered in papers by Drs. Harry Eagle, William A. Hinton, Reuben Kahn, Benjamin Kline, and John H. Kolmer, with special reference to the tests which each of these workers has described.

Need for training of laboratory personnel will be the subject of the second section. The qualifications and training for both laboratory directors and technicians will be presented in separate papers.

The third section will discuss the prosecution of the studies to evaluate the performance of serologic tests within the States. The efficiency of branch State laboratories and of municipal, hospital, and private laboratories cannot be studied on a national basis. The subject is much too large. Should this be made a function of the State or large municipal department of health? Actual experience with such studies in the States of Maryland and New Jersey and in the City of Cleveland will be described.

The fourth section will consider the desirability of licensing or approving for the performance of serodiagnostic tests for syphilis, laboratories within the States by the respective State departments of health. This discussion will be conducted from the standpoint of the private laboratory director by Dr. Frederick H. Lamb of Davenport, Iowa. The health officer's side will be presented by Dr. A. Wadsworth, State Department of Health, Albany, N. Y.

An additional feature of the meeting will be an actual demonstration of the performance of the Eagle, Hinton, Kahn, Kline, and Kolmer tests by the originators of these procedures.

Those interested in obtaining further information should write to the Surgeon General, U. S. Public Health Service, Washington, D. C.

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology, will be held in various cities of the United States and Canada on Saturday, November 5, 1938. Last day for applying is September 5.

The next general examination for all candidates (Groups A and B) will be held in St. Louis, Missouri, in June, 1939, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's Office not later than sixty days prior to the scheduled dates of examination.

Books Received

MEN PAST FORTY. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 154 pages. Harvest House, New York, 1938.

SYPHILIS, GONORRHEA, AND THE PUBLIC HEALTH. By Nels A. Nelson, Director, Division Genitoinfectious Diseases, Massachusetts Department of Public Health, and Gladys L. Crain, R. N., Epidemiologist, Division of Genitoinfectious Diseases, Massachusetts Department of Public Health. The Macmillan Company, New York, 1938.

MANAGEMENT OF THE SICK INFANT AND CHILD. By Langley Porter, Dean, University of California Medical School, and Professor of Medicine, etc., and William E. Carter, Director, University of California Hospital, Out-Patient Department, etc. Fifth revised edition, illustrated, 874 pages. The C. V. Mosby Company, St. Louis, 1938.

THE TREATMENT OF CLINICAL AND LABORATORY DATA. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By Donald Mainland, Professor of Anatomy, Dalhouse University, Halifax, Nova Scotia, Canada. With 23 text figures, 340 pages. Oliver and Boyd, Edinburgh, 1938.

THE HEART IN PREGNANCY. By Julius Jensen, Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 371 pages. The C. V. Mosby Company, St. Louis, 1938.

TWENTY-EIGHT YEARS OF STERILIZATION IN CALIFORNIA. By Paul Popenoe, Sc.D., and E. S. Gosney, B.S., LL.B. Pasadena, 1938.

THE PATIENT AND THE WEATHER. By William F. Peterson, M.D. Vol. IV. Part 3. Organic Disease—Surgical Problems. Edwards Brothers, Inc., Ann Arbor, Mich, 1938.

HEMORRHOIDS. By Marion C. Pruitt, M.D., Atlanta, Georgia. President, American Proctologic Society, Associate in Surgery, Emory University School of Medicine, etc. With 73 illustrations, including 7 in color, 170 pages. The C. V. Mosby Company, St. Louis, 1938.

SYMPTOMS OF VISCERAL DISEASE. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, M.D., Medical Director, Pottenger Sanatorium for Diseases of the Chest; Professor of Clinical Medicine, University of Southern California, etc. Fifth edition, with 87 text illustrations and 10 color plates, 442 pages. The C. V. Mosby Company, St. Louis, 1938.

ESSENTIALS OF OBSTETRICAL AND GYNECOLOGICAL PATHOLOGY, with Clinical Correlations. By Marion Douglass, M.D., Assistant Professor of Gynecology, Western Reserve University, and Robert L. Faulkner, Senior Clinical Instructor in Gynecology, Western Reserve University. With 148 illustrations, 187 pages. The C. V. Mosby Company, St. Louis, 1938.

SEX SATISFACTION AND HAPPY MARRIAGE. By the Reverend Alfred Henry Tyrer, Clergyman of the Protestant Episcopal (Anglican) Church. Foreword by Robert L. Dickinson, M.D., New York. Emerson Books, Inc., New York, 1938.

EAT AND KEEP FIT. Scientific Secrets of Diet. By Jacob Buckstein, M.D., Consulting Physician in Disease of the Stomach to Central Islip Hospital, etc. 128 pages. Emerson Books, Inc., New York, 1938.

TEXTBOOK OF CLINICAL PATHOLOGY. Edited by Roy R. Kracke, M.D., Professor of Pathology, Bacteriology and Laboratory Diagnosis, Emory University, etc. With the assistance of twelve outstanding contributors. Illustrated, 567 pages. William Wood & Company Division, Williams & Wilkins Company, Baltimore, 1938.

EL CICLO DE LA MUCOSA VAGINAL EN LA MUJER. Par Guillermo di Paola. Illustrated, 76 pages. Editor: El Ateneo, Buenos Aires, 1938.

THE ADRENAL CORTEX AND INTERSEXUALITY. By L. R. Broster, Clifford Allen, H. W. C. Vines, Jocelyn Patterson, Alan W. Greenwood, G. F. Marrian and G. C. Butler. With a foreword by Sir Walter Langdon-Brown. Illustrated, 245 pages. Chapman & Hall, Lim. London, 1938.

ANNUAL REPORT ON THE RESULTS OF RADIOTHERAPY IN CANCER OF THE CERVIX. First volume, collated in 1936. With appended Atlas. Edited by J. Heyman, Stockholm. Health Section of League of Nations. Geneva, 1937.

THE SINGLE WOMAN AND HER EMOTIONAL PROBLEMS. By Laura Hutton, physician, Tavistock Clinic, London. Second edition, 173 pages. William Wood and Co., Baltimore, 1937.

LEÇONS DU JEUDI SOIR A LA CLINIQUE TARNIER. Publiées sous la direction de A. Brindeau. Un volume, 318 pages, 66 figures. Vigot Frères, Paris, 1938.

LIÇOES DE CLINICA OBSTETRICA. Par Clovis Correa da Costa, chefe do Servicio de Ginecologia do Hospital da Fundação Gaffrée-Guinle. Livrraria Moura, Rio de Janeiro. 1938.

PROGRESSIVE RELAXATION. By Edmund Jacobson, A.M., Ph.D., M.D., Laboratory for Clinical Physiology, Chicago. 494 pages. The University of Chicago Press, Chicago, 1938.